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CONTENTS

PAGE
Potential Reversibility of Rheumatoid Arthritis. PHILIP S. HENCH 90
Adrenocortical Hormone in Arthritis. PHILIP S. HENCH AND OTHERS 97
Drugs in the Treatment of Rheumatic Diseases. N. MARCH 105
Salicylate Therapy in Rheumatic Fever. GEOFFREY WARDENER 120
Thiouracil, etc., in Experimental Polyarthritis. HELEN B. TAUSSIG AND OTHERS 125
Copper and Gold Salts in Rheumatoid Arthritis. J. FOSSERIER 132
Serum Anti-trypsins in Chronic Rheumatic Disease. HARRY COLE 135
Familial Incidence of Rheumatoid Spondylitis. BERNARD RICCOBONO AND R. H. PAYNTER 139
Aetiology of Ankylosing Spondylitis. H. J. WARD 143
Operative Arthrography of the Knee Joint. A. E. JOSLIN 149
Rheumatoid Arthritis and Anterior Uveitis. BRANSON LUCK AND OTHERS 156
Generalized Myositis Fibrosa. J. A. STRONG 158

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# EDITORIAL

Great interest has been aroused, not only in medical circles but also in the lay press, in the report that as the result of research work in the United States a new remedy for the treatment of rheumatoid arthritis has been discovered, which has given striking results in a series of cases. The clinical tests have been carried out at the Mayo Clinic, Rochester, Minnesota, and published in the Proceedings of the Staff Meetings of the Mayo Clinic. The Editors of the *Annals of the Rheumatic Diseases* take this opportunity of expressing their deep appreciation of the generosity of the Editors of the Proceedings and of the distinguished members of the team of workers, Drs. Hench, Kendall, Slocumb, and Polley, in permitting them to reproduce the original report in the Annals for the information of the medical profession in Great Britain ; sincere thanks are extended for this courtesy.

It would be out of place to discuss the details of the research in this Editorial. They must be studied in full in original report and in conjunction with the Heberden Oration which Dr. Hench delivered to that Society last October and which is now published in the *Annals*. That oration indicated some of the considerations which led to the research which were the outcome of Dr. Hench's own observations carried out over a long period of years. The microbic theory of the causation of rheumatism has long been losing ground, and the effect on arthritis of jaundice and pregnancy pointed to the probability of some basic biological disturbance and the importance of research in this direction. The temporary relief often observed after various surgical procedures causing shock, whether for the removal of infective foci, such as extensive dental extractions, tonsillectomy, etc., or for purposes unrelated to the arthritis, pointed to the possibility of this being due to adrenal action, though such a possibility was long overlooked. Selye in 1946, after various experimental procedures, produced in animals changes in the joints and in the heart similar to those observed in human beings suffering from rheumatism and put forward the idea that " the adrenal cortex may play an important role in the pathogenesis of rheumatic and rheumatoid conditions in man ". Research progressed on the lines that these observations indicated. Kendall, who had been engaged in studying the biochemistry of the adrenal cortex, was in 1948 able to supply the adrenal hormone compound named compound " E " for clinical trial by his colleagues at the Mayo Clinic, and it is this compound which Dr. Hench now reports as having given such striking results. Apart from its effect in treatment, it will stimulate research in many directions which may produce results of the utmost importance. The analogy of insulin comes to mind. The material is difficult of manufacture, and a considerable time must elapse before adequate supplies are available for research, apart from treatment on any scale ; but arrangements are in progress for a thorough trial in this country when supplies can be obtained.

While this important work must be a notable feature of this issue of the *Annals*, the valuable article by Dr. Mutch on the action of drugs in rheumatism will be found of very great interest and deserves careful study. It covers a remarkably wide range of remedies and is written in a scientific and critical spirit based on an encyclopaedic knowledge of the subject. It will be of great help to practitioners concerned with the treatment of rheumatism in all its forms.

Other articles on various aspects of the aetiology, pathology, and treatment of rheumatic disease cannot be discussed here, but they will, it is hoped, be found of interest and importance.

# THE POTENTIAL REVERSIBILITY OF RHEUMATOID ARTHRITIS*

BY

PHILIP S. HENCH

Rheumatoid arthritis has two sharply contrasting characteristics, that of potential chronicity and that of potential reversibility. The potential chronicity of rheumatoid arthritis is all too well known. Although only potential and not absolute, this characteristic has been so distressing and prominent that it has dominated medical literature for a century, and is reflected in the nomenclature and definitions of the disease and in the general similitude of textbook teachings on prognosis.

So graphically has the chronic progressive form of this disease been described that it has become almost indelibly impressed on the minds of physicians and laymen alike as the archetype, not only of rheumatoid arthritis, but of all the arthritides. Hence to most laymen a diagnosis of arthritis arouses fear of the rheumatoid type. The term "rheumatoid arthritis" has come to imply more or less relentless progression to crippledom. Hence many physicians regard arthritis which does not last long but remits more or less completely after a few weeks or months, as being not rheumatoid arthritis, but a different form worthy of special designation, such as "focal arthritis" or "infective arthritis".

The contrasting characteristic of rheumatoid arthritis, its potential reversibility, has not been sufficiently described or appreciated, but to the clinical investigator it is much more important than is its potential chronicity. From the standpoint of pathogenesis rheumatoid arthritis involves two abnormal processes which must be separated distinctly: its pathologic physiology constitutes its "fire"; its pathologic anatomy represents the "ashes" of the disease. Its pathologic anatomy, of which we know something, is largely irreversible, but its pathologic physiology, of which we have known almost nothing, is potentially, and under certain circumstances, dramatically reversible.

By potential reversibility I refer to the inherent, but too often dormant, ability of the human body to correct (at least temporarily) the abnormal or pathologic physiology underlying rheumatoid arthritis at any stage of the disease and to bring its active symptoms under control, in other words, to "put out the fire".

The inherent reversibility of rheumatoid arthritis may be activated spontaneously, therapeutically or accidentally.

### Spontaneous Reversibility

Brief comments on the spontaneous reversibility of rheumatoid arthritis can be found here and there in the older medical literature. Garrod wrote in 1876: "A patient not uncommonly had threatenings of the disease a year or two previously, which passed off in a month or two; a second premonitory attack of a severer character may have succeeded the first and in its turn . . . may have again passed off; a few months more bring on a third attack which assumes a character of greater permanency." Others have noted that the disease may subside altogether when only a few joints have become involved.

Such statements are supported by modern clinical experiences. Bauer (1943) has stated, "Recovery from the first attack is often complete and the remission may last for months or even for years; the patient may have a number of attacks before the disease becomes chronic." Ropes and Bauer (1945) say: "It seems probable that some patients have only one attack without subsequent exacerbation; the remission may last throughout life." Again, Ropes (1944) says, "The atypical milder form is equally characteristic of the disease and probably more common" than the supposedly typical chronic progressive form.

### Therapeutic Reversibility

The ability to induce slowly remissions of varying degrees and to stop the disease in time has been claimed for a host of now-discarded remedies. Most of these remissions were probably spontaneous, not therapeutically induced. To-day many rheumatologists hold the opinion that gold salts induce remissions more often and more completely than any other single therapeutic agent. Even so,

* Abstract of The Heberden Oration, delivered before the Heberden Society of London, October 15, 1948.

truly satisfactory results are in the minority, often appear tardily, and may be disappointingly transient.

An ideal remedy would provoke regularly remissions which would be prompt, " complete ", and permanent. Far inferior to such an ideal remedy, but of considerable interest to me as an investigator have been the curious reactions of many patients with rheumatoid arthritis to the following agents : foreign proteins (for example, triple typhoid vaccine), starvation, and surgery.

**Febrile Reactions to Foreign Protein.**—Many years ago as a neophyte in rheumatology I witnessed an event which I have never been able to discount or forget. On our hospital service we were then more or less habitually inducing febrile reactions to triple typhoid vaccine, generally with disappointing or equivocal results. But one day a badly disabled rheumatoid patient reacted promptly and with unusual effectiveness ; seemingly a remission of marked degree had been induced. The remission was largely sustained, and through subsequent years I have seen this patient frequently and he has had little or no arthritic activity. Such experiences have been few, but not uncommonly we have been tantalized by seeing brief periods of marked improvement after such reactions so that for a few days the patient thought himself " practically well ". Later when his brief respite was over, he would chide us ruefully, " Why can't you prolong that kind of relief ? " The cause for such relief and the reason for its rapid appearance and disappearance have remained unknown.

**Starvation.**—In 1910 Guelpa introduced a new treatment which he considered of marked value in several conditions, notably diabetes and certain forms of rheumatism or arthritis. The treatment consisted of absolute or relative starvation for variable periods of time. His results were poorly documented and largely unconvincing. But since then physicians of critical judgment have noted occasional instances in which rheumatoid arthritis seemed actually to retreat or disappear temporarily under conditions of starvation. As a practical type of treatment or even as a promising research venture, starvation lacked form and substance. Hence it has had few respectable protagonists. In the United States between 1920 and 1930 it was espoused by faddists at two or three so-called health schools.

Between 1925 and 1935 I saw at the Mayo Clinic 5 patients who, having had rheumatoid arthritis for from two to eight years, had fasted a total of fourteen times for periods ranging from three to twenty-one days. Marked relief presumably resulted after two or three days of fasting, but disappeared as soon as the fast was discontinued. Willing to demonstrate the phenomenon to me, one of these patients fasted for eight days and appeared to obtain notable subjective relief. Certain joints became painless, but an ankle remained tender, and the sedimentation rate was not favourably affected.

**Surgery.**—The twentieth century to date has been notable for the number of surgical procedures advocated for rheumatoid arthritis. How often has *bona fide*, if transient, relief appeared to follow tonsillectomy, only to fade after two or three weeks ! In the same category probably belong the supposed results of hysterectomy, bone-puncture, certain operations on the colon, thyroidectomy, cholecystectomy, parathyroidectomy, splenectomy, sympathectomy, and others. That such diverse, unrelated procedures are commonly followed by transient amelioration of rheumatoid arthritis will be admitted by most experienced observers. But how can each of these procedures *specifically* affect the entity, rheumatoid arthritis ? None of these procedures has, in my opinion, any specific merit. But they may possess some common denominator, in that they may motivate a biologic reaction which, though helpful to the patient, bears no inseparable relationship to the surgical manipulation momentarily chosen as the agent of relief.

Considered responsible for this transient, sometimes relatively prolonged postoperative relief have been each of the following : the removal of foci of infection, an improved articular circulation, the correction of some endocrine abnormality, postoperative rest in bed, postoperative shock, postoperative fever or starvation, or the chemical effect of anaesthesia.

In 1930 at the Mayo Clinic we studied the analgesia and the improved circulation which often followed lumbar sympathectomy for the relief of rheumatoid arthritis of the lower extremities. But since the upper extremities, whose sympathetic nerve supply was surgically untouched, were often temporarily relieved almost as much as the surgically affected lower extremities, we concluded that the general anaesthesia incident to the surgical procedure may have been important and that the common denominator of diverse surgery might concern the anaesthesia more than any particular operative procedure. Later, at the Mayo Clinic, Slocumb (personal communication) investigated the effect of various anaesthetic agents given alone to several volunteers with rheumatoid arthritis. Of these patients who were anaesthetized for fifteen to thirty minutes, 60 per cent. had definite objective and subjective articular improvement for a week or more, an additional 20 per cent. had definite

subjective improvement (with or without objective improvement) for only two or three days and the remaining 20 per cent. were unaffected. When relief occurred, the patient noted it as soon as he wakened from the anaesthesia, and it resulted even though no febrile reaction accompanied the anaesthesia.

### Accidental Reversibility

Much more dramatic and interesting than the relatively feeble remissions induced by foreign-protein reactions, starvation, or surgery, or even than the sturdier remissions induced by chrysotherapy, are those which may arise accidentally, appearing in connexion with coincidental pregnancy or jaundice. These two conditions are usually potent antagonists of rheumatoid arthritis. In the presence of either one rheumatoid arthritis finds it difficult to progress, or indeed to do otherwise than to beat a rather precipitous retreat.

**Remissions Induced by Pregnancy.**—For years observers, noting the greater incidence of rheumatoid arthritis in women, especially in those between 20 and 40 years of age, have speculated as to the relation of this disease to menses, pregnancy, and the postpartum state. The literature of the past century contains scattered references to the subject, generally only a sentence here or a paragraph there. Between 1845 and 1938 opinions regarding the effect of pregnancy were contradictory. It was variously stated that rheumatoid arthritis may be precipitated by, or first appear during pregnancy, be aggravated by pregnancy, be unaffected thereby, or be partially or completely relieved during pregnancy. No critical investigation was ever undertaken to clarify these confusions.

Having noted on many occasions an amelioration of rheumatoid arthritis during pregnancy and conjecturing that this phenomenon was analogous to, if not identical with, that which may occur in the jaundiced arthritic patient, I reported (Hench, 1938a) observations on the effect of thirty-four pregnancies on twenty patients with rheumatoid arthritis. Thirty of the thirty-four pregnancies produced marked or complete remission of the arthritis. Three of the four ineffectual pregnancies were presumably normal; the fourth was an ineffective tubal pregnancy terminated at its sixth week in a woman who had experienced the phenomenon of relief early in four of her five (four intra-uterine, one tubal) pregnancies even though her pregnancies proceeded to term only once.

Since this report Slocumb, Polley, and I have recorded the results of pregnancy in a total of about 150 rheumatoid patients. A preliminary summary indicates that most of these patients were markedly improved or completely relieved during normal pregnancy. A few received little or no relief from what were apparently normal pregnancies. Rheumatoid arthritis rarely began during pregnancy; in exceptional cases it made a brief appearance during pregnancy, then quickly retreated to return at a more favourable (postpartum) period. Rheumatoid patients relieved once by pregnancy were almost always relieved by subsequent intra-uterine pregnancies whether the latter were carried to term or ended (after the third month) by miscarriage or abortion. Some patients experienced relief with each of three to five pregnancies; one patient had relief with each of nine pregnancies.

Rheumatoid patients not relieved once by (normal ?) intra-uterine pregnancy were usually not relieved by subsequent pregnancies. Most intra-uterine pregnancies produced amelioration. Some women with rheumatoid arthritis who habitually miscarried near the end of the second or third month of gestation, nonetheless had obtained marked or complete relief of articular symptoms about a month prior to the miscarriages. In certain others who tended to miscarry late in pregnancy, the phenomenon of relief was abnormal, tardy, or incomplete. Thus the early appearance of the phenomenon of relief of arthritis is no guarantee that the pregnancy will terminate normally, nor is what appears to be a normal pregnancy always associated with the phenomenon of relief. From our limited observations of such unusual cases we can perhaps conclude that a pregnancy may be constitutionally (chemically) "abnormal" even though it is locally (intra-uterine) normal.

Articular amelioration began usually about the fourth to the sixth week of pregnancy, sometimes later. Relief began during the first trimester in about 90 per cent., in the second trimester in about 10 per cent. of the patients who had amelioration. In such cases articular pain usually disappeared completely, articular tenderness subsided notably or entirely, muscular stiffness disappeared or was notably lessened, and even articular swelling was reduced markedly, sometimes completely. The phenomenon of articular relief ended usually within one to seven weeks postpartum; in some cases between the eighth and twelfth week, and in a few four to twenty-four months after parturition.

Based on the experiences in the majority of the cases analysed to date, the phenomenon of relief can be expressed tentatively by the following formula: typical pattern of relief $= 5 \pm 1$ week postconception to $4 \pm 3$ weeks postpartum. Each patient tended to exhibit a formula or pattern

of relief which was consistent for that individual. With certain variations, the formula of relief was fairly constant for more than half the entire group. But many others exhibited atypical patterns of relief. The postpartum return of articular symptoms did not appear to be governed by the length of time in bed, by the duration of lactation, or by the approach of the first postpartum menses.

**Remissions Induced by Hepatitis with Jaundice.**—The second and even more dramatic type of accidental remissions is motivated during the course of hepatitis with jaundice. The first experience of this kind came to my attention on April 1, 1929. Since then I (1933, 1934, 1938b, c, 1940) have studied this phenomenon as it occurred in twenty-five, and as it failed to occur in five more, jaundiced patients. Of these thirty patients with rheumatoid arthritis who had various types of spontaneous intercurrent jaundice twenty-five (83 per cent.) experienced marked or complete temporary remission of the arthritis irrespective of the concentrations of bilirubin in serum. When the level of serum bilirubin rose to more than 6 or 8 mg. per 100 c.cm., the phenomenon of relief almost always occufred (in twenty-five, or 96 per cent., of twenty-six such cases). When relief was induced, it was complete in 68 per cent., marked but incomplete in the rest.

Since my initial observations fifteen reports by others have concerned twenty-three jaundiced rheumatoid patients, twenty-two (96 per cent.) of whom obtained relief. Sometimes the intensity of the jaundice was not stated. Recently Holbrook (1948) collected from the literature and by questionnaires sent to certain rheumatologists a total of eighty-four cases of rheumatoid arthritis in which jaundice supervened. In fifty-four (64 per cent.) of these cases a marked remission occurred. Had this report concerned only those in which concentrations of serum bilirubin were more than 6 mg. per 100 c.cm., undoubtedly the percentage of cases in which jaundice was effective would have been notably higher.

Although a certain intensity of jaundice must be attained before the phenomenon of articular relief is activated, bilirubin is not the responsible agent. Several types of jaundice have shown themselves to be effective provided that the liver was damaged enough to produce a fairly notable bilirubinaemia of the direct-reacting type : so-called catarrhal jaundice ; spontaneous intrahepatic jaundice ; jaundice induced by cinchophen, by transfusions, by homologous serum therapy or by neoarsphenamine ; and obstructive jaundice from stones or malignancy. Jaundice associated with chryso-therapy has been effective in some cases, ineffective in others even in the presence of notable bilirubinaemia. Haemolytic jaundice appears to be ineffective. In haemolytic jaundice the serum bilirubin is of the indirect-reacting type and is rarely in notable concentrations. In my own cases the effective jaundice lasted an average of eight weeks. The articular remissions lasted from one and a half to eighty-two weeks. The remissions observed by others also varied in length, from one month to two years.

**Significance of the Potential Reversibility.**—Such observations on the potential reversibility of rheumatoid arthritis have caused a revision of our thinking on the diagnosis, aetiology, prognosis, and treatment of the disease. Since rheumatoid arthritis is sometimes reversible even in its late progressive stages, it should be regarded as potentially reversible at any stage, and probably more reversible in its early stages. That the latter is true is shown by the fact that most remedies are more effective in early stages.

A diagnosis of atypical rheumatoid arthritis should be considered more often in cases of : non-traumatic hydrops of a knee or knees, lasting a few weeks and disappearing without residues ; polyarticular or oligo-articular asymmetrical involvement, or of non-traumatic chronic monarthritis with no clinical evidence of tuberculosis ; short afebrile or febrile bouts of arthritis which are precipitated by certain acute infections and which may disappear fairly soon without articular residues, and transient articular swellings which last a few days or weeks and affect one joint one time, another joint the next time.

Any theory on the aetiology of rheumatoid arthritis must take into account the powerful ameliorative influence of jaundice and pregnancy. It has become increasingly difficult for me to harmonize the microbic theory with such amelioration. It has become easier for me to consider that rheumatoid arthritis may represent, not a microbic disease, but a basic biochemical disturbance of unknown type which is accidentally and transiently corrected by some incidental biologic change common to a number of apparently unrelated events, most notable of which are jaundice and pregnancy.

Since within the patient who has even the severest rheumatoid arthritis powerful corrective forces lie dormant awaiting the proper stimulation, the pessimism regarding prognosis, still all too prevalent, should be abandoned. The problems of practical and investigative therapeutics should be approached with new vigour and new points of view. Perhaps

the removal of a focus of infection, never a " specific remedy ", is sometimes beneficial because it may initiate a helpful biochemical reaction which has nothing to do with germs or immunity. The results of starvation and anaesthesia should be appraised by newer scientific methods. Perhaps an attempt to discover some biochemical denominator common to all these procedures, but especially to jaundice and pregnancy, would be a guide to an improved treatment for rheumatoid arthritis.

### Therapeutic Investigations Based on these Observations

Since the ameliorating effects of jaundice and pregnancy were first described, attempts have been made to obtain similar relief by several related procedures. Some physicians, impressed by the effects of pregnancy, and unaware of, or less impressed by the effects of jaundice, have investigated measures related to pregnancy. Other physicians, intrigued by the effects of jaundice, but unaware of, or unattracted by those of pregnancy, have confined their investigations to measures allied to jaundice.

**Therapeutic Pregnancy.**—Several of my patients, temporarily relieved by one pregnancy, deliberately became pregnant again in the hope that the effect might finally " stick ". Most of them were again temporarily relieved ; none were cured. Recently Holbrook recommended pregnancy in certain cases of progressive rheumatoid arthritis. In my opinion, a decision favouring further pregnancies should be based on factors other than the desire for transient articular relief, such factors being the parents' desire for more children, and their physical and financial ability to care for them in the face of the probability that the arthritis will return after childbirth.

**Female Hormones.**—Hoping to reproduce the beneficial effects of pregnancy, several physicians have administered to non-pregnant women with rheumatoid arthritis fairly large doses of female hormones. The results to date have been almost uniformly disappointing.

To three or four volunteers with rheumatoid arthritis, Bauer (personal communication) recently gave the daily output of urine from women in the last trimester of pregnancy. The urine was passed through a Berkefeld filter, disguised as to taste, and given in " cocktail " form in repeated doses daily for four to eight weeks. No beneficial or harmful effects were noted.

**Transfusions of Blood from Pregnant Women.**—In 1941 and 1947 Barsi-Basch reported that he had induced prolonged remissions or marked improvement in 64 per cent. of twenty-eight rheumatoid patients to whom he had given small transfusions of blood from pregnant women. In contrast to these results have been those noted in five other reports which concerned a total of eighty-five patients, none of whom were cured by transfusions of such blood. Although a few appeared to be somewhat relieved for a while, the majority received little or no relief.

Having noted several years ago (Hench, 1938b) that transfusions of blood of deeply jaundiced persons did not benefit a few rheumatoid volunteers and that no antirheumatic " substance X " could apparently be transferred passively thereby, I discarded the idea of using blood from pregnant women also. However, my associate, Dr. Slocumb, did administer repeatedly to one of our patients with severe rheumatoid arthritis small amounts of serum from a pregnant woman, without significant results. Having frequently seen rheumatoid arthritis that had been relieved by pregnancy return after parturition, I find it difficult to understand how the method of Barsi-Basch can induce a prolonged remission or cure. If a pregnant woman is not cured of rheumatoid arthritis by the effects of thousands of cubic centimetres of her own (transiently effective) blood circulating within her body (and joints) for nine long months, how can that same or another woman, when non-pregnant, be cured by a few hundred cubic centimetres of the blood of another pregnant woman which can survive in the recipient for only a few weeks at most ?

But the supposed results from transfusions of blood of pregnant women can be evaluated best by comparing them with those from transfusions of normal blood. During the last seventeen years this procedure has been occasionally recommended with mild enthusiasm by a few workers. Results have often been satisfactory but rarely dramatic. It can be concluded that transient benefit occasionally results from transfusions of blood whether from non-pregnant or pregnant donors. But so far the superiority of blood from pregnant donors remains to be proved.

**Jaundice and Related Procedures.**—Reported elsewhere (Hench, 1938b, c ; 1940) as being ineffective were : bile salts given orally, synthetic bile salts (decholin) given orally or intravenously, human bile given by stomach tube, or bile given by proctoclysis, liver extracts given parenterally, cysteine, heparin, transfusions of blood of deeply jaundiced donors, high-fat diets given to induce hyperlipaemia or hypercholesteraemia, and haemolytic jaundice induced by the oral administration of toluenediamine. Also generally ineffective was the hyperbilirubinaemia induced by the intravenous

administration of bilirubin alone or with decholin (Hench, 1938b, c ; 1940 ; and Thompson and Wyatt, 1938). Of limited effectiveness but of considerable scientific interest have been the results of jaundice induced by the administration either of icterogenic serum or lactophenin to volunteers with rheumatoid arthritis.

Notable articular remissions were produced in thirty-three of forty arthritic patients given icterogenic serum to induce jaundice (MacCallum and Bradley, 1944 ; Gardner and others, 1945 ; Rennie and Fraser, 1946). The articular remissions were complete but transient in at least eleven of the thirty-three cases of effective jaundice. For the clinical investigator this type of jaundice has two great drawbacks : the percentage of successful inoculations is small (only 7 to 10 per cent.) ; the incubation period between inoculation and development of jaundice is long (27 to 131 days).

A more useful type of jaundice for the investigator is that induced by the oral administration of lactophenin as reported by Hanssen in 1942 and investigated by me. Jaundice, characterized by an effective bilirubinaemia of the direct-reacting type, was promptly induced by Hanssen in four of seven, by me in three of nine, arthritic volunteers. Whenever jaundice was produced, notable articular remissions occurred promptly. In one patient I induced jaundice with lactophenin twice with marked improvement of joints each time. Articular relief occurred with lower concentrations of bilirubinaemia than have usually been effective in spontaneous jaundice. But the articular remissions have not been permanent.

### Comments on the Mechanism of Relief

In considering the probable mechanism of relief of rheumatoid arthritis from these diverse, seemingly unrelated agents, I will use an analogy. Diabetes of a certain patient could be " controlled " in 1920 by attention to diet, in 1922 by injections of a medicine (insulin), and perhaps in 1950 by the coincident and fortuitous appearance of an insulin-producing pancreatic tumor. Yet the agent in each of these apparently different mechanisms would be, of course, the same. The common denominator of diet, medicine, and tumour would be an equilibrium between the need and the supply of insulin.

It seems equally logical to suppose that the ultimate agent producing articular relief in jaundice is closely related to, if not identical with, that responsible for articular relief in pregnancy. If so, the responsible agent is neither bilirubin nor a unisexual (female) hormone.

My use of lactophenin jaundice has been, not an end in itself, but a means to an end. By studying the biochemical alterations which occur during and after the articular remissions produced by induced jaundice, and by comparing them to those which may be found to coincide regularly with the pattern of articular relief during pregnancy, perhaps we may find a clue to some factor of prime aetiological and therapeutic significance. If this antirheumatic " substance X " be a biologic compound specific in nature and function, as it may well be, we have had no clue as to the organ of its origin.

TABLE

AMELIORATION BY PREGNANCY OR JAUNDICE

| Conditions | Relieved by | |
|---|---|---|
| | Pregnancy | Jaundice |
| Rheumatoid arthritis | + | + |
| Chronic arthritis with psoriasis (skin unrelieved) | | + |
| Psoriatic arthritis (skin unrelieved) | + | ++ |
| Psoriasis (no arthritis) | ++ | |
| Intermittent hydrops, " true " | + | |
| Intermittent hydrops, symptomatic, with rheumatoid arthritis | + | |
| Fibrositis, primary | + | + |
| Asthma | ++ | ++ |
| Migraine | ++ | + |
| Hay fever | ++ | + |
| Addison's disease | ++ | |
| Myasthenia gravis | ++ | |

\+ Cases encountered by P.S.H.
++ Cases reported by others.

**Other Conditions Ameliorated by Pregnancy or Jaundice or Both.**—Certain other conditions besides rheumatoid arthritis and primary fibrositis are often, but not always, relieved by pregnancy or jaundice or both (see Table) (Hench, 1940). Obviously, the phenomenon of relief is not disease-specific. It appears to be group-specific which should lead to an increase, rather than a decrease, in efforts to elucidate the mechanisms of relief.

Although it seems logical to assume that jaundice and pregnancy may motivate the same mechanism of relief so far as rheumatoid arthritis is concerned, it does not necessarily follow that all the conditions listed in the Table are influenced in an identical way. Pregnancy and jaundice are accompanied by a multitude of specific and incidental (non-specific) biochemical alterations. One specific or non-specific deviation may benefit patients with one disease, another deviation may effect another disease. But attention to this list may be a guide in future investigations.

## Conclusion

These clinical and investigative observations have fortified my belief that rheumatoid arthritis is not necessarily a relentless, chronic progressive condition which will never have a truly satisfactory, rapid method of control. Rheumatoid arthritis is even now potentially, rapidly reversible at any stage of the disease and eventually will become therapeutically reversible or rapidly controllable. The powerful corrective forces which lie dormant within every patient with this disease await the superior stimulus of the future. Meanwhile, they can be set in motion, inconstantly and apparently inconsistently, in a variety of ways: spontaneously, accidentally, and therapeutically.

Chrysotherapy will induce striking remissions in only about 10 or 15 per cent. of cases. From a combined programme of therapy (gold, physical therapy, removal of foci of infection, rest, and nutritious diet) striking results are *promptly* obtained in not more than about 15 per cent. of cases.

Compare the potency, or relative impotency, of these remedies, the best we have, with that inherent in jaundice or pregnancy which induces marked articular remissions in about 60 to 90 per cent. of cases. Obviously there exists a great unrealized potential for the relief of rheumatoid arthritis, a potential we must bring to reality. Rheumatoid arthritis does have its "Achilles' heel" against which new offensives must be directed. Let us exploit the demonstrated points of weakness with renewed optimism and zeal.

### References


Barsi, I. (1947). *Brit. med. J.*, **2**, 252.
——, (1941). *Orvosi Hetilap*, **42**, 85.
Bauer, W. (1943). *New Engl. J. Med.*, **229**, 583.
——. Personal communication to the author.
Gardner, Frances, Stewart, Alice, and MacCallum, F. O. (1945). *Brit. med. J.*, **2**, 677.
Guelpa, G. (1910). *Ibid.*, **2**, 1050.
—— (1914). "Auto-intoxication and Disintoxication; an Account of a New Fasting Treatment in Diabetes and Other Chronic Diseases," p. 152. Rebman Company, New York.
Hanssen, P. (1942). *Acta med. scand.*, **109**, 494.
Hench, P. S. (1933). *Proc. Mayo Clin.*, **8**, 430.
Hench, P. S. (1934). *Ann. int. Med.*, **7**, 1278.
—— (1938a). *Proc. Mayo Clin.*, **13**, 161.
—— (1938b). *Arch. intern. Med.*, **61**, 451.
—— (1938c). *Brit. med. J.*, **2**, 394.
—— (1940). *Med. Clin. N. Amer.*, **24**, 1209.
Holbrook, W. P. (1948). *N.Y. Med.*, **4**, 7.
MacCallum, F. O., and Bradley, W. H. (1944). *Lancet*, **2**, 228.
Rennie, J. B., and Fraser, T. N. (1946). *Glasgow med. J.*, **27**, 157.
Ropes, Marian W. (1944). *Arch. phys. Therap.*, **25**, 397.
——, and Bauer, W. (1945). *New Engl. J. Med.*, **233**, 592.
Slocumb, C. H. Personal communication to the author.
Thompson, H. E., and Wyatt, B. L. (1938). *Arch. intern. Med.*, **61**, 481.


## La Reversibilité Potentielle de l'Arthrite Rhumatismale

### Conclusion


Ces observations cliniques et investigatrices ont renforcé ma conviction que l'arthrite rhumatismale n'est pas nécessairement une affection implacablement chronique et progressive, vouée à n'être jamais maîtrisée par un procédé rapide et vraiment satisfaisant. Potentiellement, l'arthrite rhumatismale est même à présent rapidement reversible à n'importe quel stade de la maladie et elle finira bien par devenir thérapeutiquement reversible ou rapidement maîtrisable. Les puissantes forces correctrices sommeillant dans chaque individu atteint de cette maladie attendent le stimulant supérieur de l'avenir. Entretemps, celui-ci peut etre déclanché d'une façon inconstante et apparemment inconséquente de manières différentes: spontanée, accidentelle, et thérapeutique.

La chrysothérapie produira une rémission frappante dans 10 à 15 pour cent des cas. En employant tout l'arsénal thérapeutique (or, physiothérapie, élimination des foyers d'infection et régime alimentaire) on n'obtient promptement de résultats frappants que dans environ 15 pour cent des cas.

Comparons la puissance, ou la relative impuissance, de ces rémèdes, les meilleurs en notre possession, à celle inhérente à l'ictère ou à la grossesse, qui amène des rémissions articulaires considérables dans environ 60 à 90 pour cent des cas. Manifestement, il y existe un potentiel, non réalisé, susceptible de soulager l'arthrite rhumatismale; un potentiel qu'il nous faut faire ressortir. L'arthrite rhumatismale a son "talon d'Achille" contre lequel il nous faut diriger tous les nouveaux assauts. Exploitons les points faibles que nous venons de montrer avec un renouveau de zèle et d'optimisme.

# THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS*

## PRELIMINARY REPORT

BY

PHILIP S. HENCH, EDWARD C. KENDALL, CHARLES H. SLOCUMB, and HOWARD F. POLLEY

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The adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone, hereinafter called "compound E" (Mason and others, 1938; Reichstein and Shoppee, 1943) has been administered to fourteen patients with severe or moderately severe rheumatoid arthritis. In each case improvement in clinical features and in sedimentation rates began to occur within a few days. When administration of the hormone was discontinued, the disease generally relapsed promptly.

Essentially similar clinical results accompanied by various biochemical effects were obtained from the administration of the pituitary adrenocorticotrophic hormone to two patients.

The rarity of these compounds presently and in the immediate future, and the limited scope of our preliminary data (especially regarding prolonged administration) make inappropriate now the use of the term "treatment" except in an investigative sense. This paper is presented, not as a clinico-therapeutic report, but as a study of certain physiologic effects which these new hormones exert on rheumatoid arthritis.

### Antecedent Work

Since 1929 one of us (Hench, 1933, 1934, 1935, 1938a, b, c, 1940, 1949) has studied the beneficial effects of pregnancy and jaundice on rheumatoid arthritis. Results of these and other studies led us to the following conclusions. Even though the pathologic anatomy of rheumatoid arthritis is more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so. Within every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation. Therefore, the disease is not necessarily a relentless condition for which no satisfactory method of control should be expected. The inherent reversibility of rheumatoid arthritis is activated more effectively by the intercurrence of jaundice or pregnancy than by any other condition or agent thus far known. Regardless of the supposed "validity" of the microbic theory, rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical.

It became increasingly difficult to harmonize the microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy. It became easier, rather, to consider that rheumatoid arthritis may represent, not a microbic disease, but some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events. It seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not identical with, that which relieves the same disease in jaundice; if so, it could be neither hyperbilirubinaemia nor a unisexual (female) hormone since neither of these is common to both pregnancy and jaundice. It was believed that the discovery of some biochemical denominator common to various agents or states beneficial in rheumatoid arthritis, but common especially to jaundice and pregnancy, would provide us with an improved treatment or control of the disease.

Finally, it was conjectured that the hypothetic common denominator or "antirheumatic substance X" was not a disintegration product from a damaged liver, but probably was a biologic compound specific in nature and function, a compound which was normal to the human organism (Hench, 1935, 1949). But if this was true, we had no certain clue as to its chemical nature or the organ of its origin.

* Reprinted from the *Proceedings of the Staff Meetings of the Mayo Clinic* by kind permission of the Editor and the authors.

### Earlier Investigative Therapy

In an attempt to reproduce the effects of jaundice or pregnancy we and others used more or less empirically, many agents and measures, some related to jaundice, some to pregnancy. These included the transfusion of blood from jaundiced (Hench, 1938b) or pregnant donors (Barsi, 1947), the administration of female hormones and various biliary products (Hench, 1938b), the production of experimental hyperbilirubinaemia (Hench, 1938c; Thompson and Wyatt, 1938) and of induced jaundice by means of toluylene diamine (Hench, 1938b), icterogenic serum (MacCallum and Bradley, 1944; Gardner and others, 1945; Rennie and Fraser, 1946), or lactophenin (Hench, 1949; Hanssen, 1942). The latter two agents produced articular remissions, but the mechanism of relief was not apparent.

In time we conjectured that the antirheumatic substance X might be an adrenal hormone. This conjecture was strengthened by the knowledge that temporary remissions of rheumatoid arthritis are frequently induced by procedures which are now known to be capable of stimulating the adrenal cortices, such as general anaesthesia or surgical operation (Hench, 1949). In 1938 we administered to several rheumatoid volunteers lecithin separated from the adrenal gland, not as an adrenal product *per se*, but in an attempt to induce hyperlipaemia such as may occur in association with pregnancy and jaundice. In January 1941 we recorded our interest in adrenal cortical fractions in general and in Kendall's compound E in particular, and we used briefly Kendall's cortical extract. But compound E was not available to us until September 1948. In requesting a supply for our investigation from Merck and Co., Inc.,* we expressed the belief that if any adrenal compound was in fact the agent by which rapid amelioration of rheumatoid arthritis by jaundice or pregnancy is accomplished, "we would expect to see some results within a very few days".

### Compound E for Rheumatoid Arthritis

**Initial Case.**—The first patient for whom compound E was used was a married woman 29 years old who had severe rheumatoid arthritis of four and a half years' duration. She had not responded satisfactorily to many treatments. She was admitted to the Mayo Clinic and the hospital on July 26, 1948. Many joints were stiff, swollen, tender, and painful on movement. Radiographs revealed destructive changes in her right hip, because of which she limped, and less extensive changes in other joints. The sedimentation rate (Westergren), 75 mm. on July 27, increased and was 109 mm. on Aug. 24, and 108 on Sept. 3.

She volunteered to take lactophenin orally, in the hope that jaundice would result and produce a significant remission. But jaundice did not develop, and no significant clinical or biochemical alterations occurred.

On Sept. 20 the patient's joints were worse than they had been. On Sept. 21 she could hardly get out of bed. On that day we began the daily intragluteal injection of 100 mg. of compound E. During that day no change was apparent; walking was so painful that she ventured only once from the room. On Sept. 22 her improvement did not appear significant to us. But when she awoke on Sept. 23 she rolled over in bed with ease, and noted much less muscular soreness. On Sept. 24, painful morning stiffness was entirely gone. Scarcely able to walk three days previously, the patient now walked with only a slight limp. Her appetite was increased.

By Sept. 27, a week after the administration of compound E was begun, articular as well as muscular stiffness had almost completely disappeared, and tenderness and pain on movement, and even swellings, were markedly lessened. The next day she shopped downtown for three hours, feeling tired thereafter, but not sore or stiff. Menses began on Oct. 1 and were unaccompanied by her usual menstrual flare-up in joints.

After eight days of use of a daily dose of 100 mg., the dose was reduced to 50 mg. daily for four days, then 25 mg. daily for ten days. But these doses were inadequate. Rheumatic symptoms increased. The sedimentation rate, which had decreased (slower than in later cases or than later in this case) from 111 to 86, increased to 118. The subsequent course of this patient will be discussed hereinafter.

**Selection of Patients.**—Since the fall of 1948 we have given compound E more or less continuously to five rheumatoid patients, and for periods of eight to sixty-one days to nine other patients; a total of fourteen patients.* None had mild or moderate disease. All had "moderately severe" or "severe" chronic polyarticular rheumatoid arthritis of four and a half months' to five years' duration, not satisfactorily responsive to much previous therapy. Three patients whose disease was of relatively short duration (4·5, 5, and 5 months) were already considerably disabled by rapidly progressive arthritis.

The condition of our first two patients was among the worst: one walked with considerable difficulty; the other had polyarthritis of many peripheral joints and rheumatoid spondylitis. The third patient had been using crutches for seven months. The fourth, ninth, and tenth patients were temporarily bedridden by acute flare-ups; the seventh patient was using a wheel chair except for a few halting steps. Two of the patients had early flexion deformities of knees. Some were ambulatory,

* Merck & Co., Inc., who have supplied compound E for this study have expressed their regret that because of the exigencies of manufacture no supplies of compound E are expected for treatment or additional research until some time in 1950 at the earliest, at which time supplies still will be exceedingly small.

* Two more patients with rheumatoid arthritis are now receiving compound E acetate (see Table).

but required help to get in or out of bed or off the toilet.

Sedimentation rates, before the use of compound E, were (in the order of cases) : 108, 118, 51, 37, 65, 47, 103, 50, 81, 115, 64, 68, 71 and 62, mm. in one hour (see Table).

**Method of Study.**—To avoid undue reliance on subjective improvement, we, before, during and after giving compound E, used special charts for the examination of joints, and made moving pictures of all patients to show their changing condition. Many biochemical tests were made. Five of the patients were studied in the metabolic unit of the Mayo Clinic.

**Controls.**—To provide adequate controls, the intragluteal injection of compound E was in some cases preceded, and in other cases replaced, by the injection of a fine aqueous suspension of cholesterol (100 mg. used daily for six to twenty-four days) indistinguishable in appearance from compound E. The times when the control solution and the adrenal hormone were interchanged were unknown to the patients and were, for five weeks, unknown even to the three clinical authors who were evaluating the results. When injection of the control solution was first commenced, no outstanding clinical or biochemical alterations occurred until the control solution was replaced by the cortical hormone. Likewise, when the hormone was replaced by the

TABLE 1

CERTAIN CLINICAL AND LABORATORY EFFECTS OF COMPOUND E AND OF ACTH ON RHEUMATOID ARTHRITIS

| | | | Chronic arthritis | | | | Sedimentation rates | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Effect of hormone : rate reduced, mm. | | | Increase in rate, mm., after hormone discontinued* | |
| Case | Sex | Age | Duration | Severity | Administration of compound E or E acetate, duration | Initial clinical improvement results; degree of | From | To | After | To | After |
| 1 | F. | 29 | 4½ yr. | Severe | 6 months | Marked | 108 | 26 | 3 mo. | Use of hormone just discontinued | |
| 2 | M. | 41 | 5 yr. | Severe | 1st period: 11 wk.<br>2nd period: 3 mo. | Marked<br>Marked | 118<br>114 | 50<br>59 | 8 wk.<br>11 wk. | | |
| 3 | M. | 64 | 3 yr. | Severe | 1st period: 60 days<br>2nd period: 14 wk. | Marked<br>Marked | 51<br>96 | 8<br>13 | 22 days<br>22 days | | |
| 4 | M. | 41 | 2 yr. | Moderately severe | 1st period: 12 days<br>2nd period: 36 days | Marked<br>Marked | 37<br>43 | 16<br>11 | 15 days<br>6 days | | |
| 5 | M. | 34 | 4½ mo. | Very severe | 3 months | Very marked | 65 | 11 | 12 days | | |
| 6 | F. | 49 | 3 yr. | Severe | 10 days | Marked | 47 | 14 | 10 days | 70 | 12 days |
| 7 | F. | 53 | 2 yr. | Moderately severe | 24 days | Very marked | 103 | 14 | 30 days | 58 | 11 days |
| 8 | M. | 62 | 5 mo. | Severe | 9 days | Very marked | 50 | 10 | 9 days | 38 | 8 days |
| 9 | F. | 44 | 2 yr. | Severe | 25 days | Very marked | 81 | 17 | 17 days | 76 | 5 days |
| 10 | M. | 49 | 5 mo. | Moderately severe | 61 days | Marked | 115 | 13 | 35 days | | |
| 11 | F. | 40 | 5 yr. | Moderately severe | 8 days | Very marked | 64 | 14 | 10 days | 70 | 20 days |
| 12 | F. | 43 | 10 mo. | Moderately severe | 42 days | Marked | 68 | 22 | 11 days | | |
| 13 | F. | 31 | 4 yr. | Moderately severe | 30 days | Marked | 71 | 13 | 26 days | | |
| 14 | F. | 45 | 5 yr. | Moderately severe | 21 days | Marked | 62 | 31 | 21 days | | |
| 15 | M. | 29 | 3 yr. | Severe | † | | | | | | |
| 16 | M. | 49 | 10 mo. | Very severe | † | | | | | | |
| Two patients (6 and 14) who also received ACTH | | | | | | | | | | | |
| 6 | F. | 49 | 3 yr. | Severe | 12 days | Very marked | 78 | 5 | 12 days | 90 | 9 days |
| 14 | F. | 45 | 5 yr. | Moderately severe | 12 days | Very marked | 93 | 18 | 9 days | 85 | 6 days |

* When rates in this column are not given, either the patient was still receiving compound E or its use had just been discontinued.
† Started April 3, 1949. Clinical results not mentioned in discussion.

control solution, articular and muscular symptoms recurred within a few days and sedimentation rates rose.

**Preparations of Compound E.**—Preparations used since December 1948 have been of greater chemical uniformity and perhaps of greater potency than those used earlier. The early preparations used for our first three patients were potent and devoid of side effects. Then certain difficulties were encountered. For reasons which are not clear, articular flare-ups promptly occurred and sedimentation rates rose quickly, coincident with the use of two different preparations. Other problems were overcome. In earlier preparations the crystals were fairly large, a possible cause of delayed absorption. Special techniques have provided suspensions of small crystals, 5 to 10 microns in size, easier to administer and to absorb. The crystals have been suspended in saline solution in a concentration of 25 mg. per cubic centimetre.

Between September 1948 and January 19, 1949, we used compound E. We then discovered that the less expensive and more easily prepared E acetate was absorbed with sufficient promptness. Since then we have used E acetate.

The preparation of the compound E used in this work has represented a co-operative effort of considerable magnitude by research chemists of Merck and Co., Inc., and by Kendall and his associates of this Clinic. Our special appreciation is due to Dr. Randolph Major, Vice-President, to Dr. James M. Carlisle, medical director, and their associates of Merck and Co., Inc. Despite intense effort, our supplies of compound E have been strictly limited because its preparation by present methods is very difficult, time-consuming, and expensive. Many uncertainties and inadequacies in this preliminary report have resulted from our inability in some cases to increase the dose at critical points, and in other cases to continue any medication after an allotted few days.

**General Plan of Dosage.**—With little to guide us except the experience of Sprague and his associates (unpublished) with two addisonian patients who received 50 and 100 mg. respectively of compound E acetate daily, we fortunately started using 100 mg. daily. We have since found that smaller daily doses of 25 to 50 mg. are generally inadequate or ineffective. To date we have no definite evidence that multiple small doses are superior to one large daily dose of either compound E or its acetate.

In earlier cases the total dose of compound E used on the first day was the same (100 mg.) as that used on later days. One hundred milligrammes of E acetate is the chemical equivalent of about 89 mg. of compound E. Because of the slightly higher molecular weight and slower absorbability of the acetate, we administered in later cases 300 mg. of acetate on the first day, and usually 100 mg. daily thereafter. This scheme gives better results, but probably will be improved.

After we obtained in each case the initial optimal improvement from this scheme of dosage (generally within seven to fourteen days), we reduced the daily dose in several cases to 75, 50, or even 25 mg., hoping to find a small, economical, effective "maintenance dose". Generally, articular flare-ups occurred and sedimentation rates rose promptly. So far a minimal daily dose of 75 to 100 mg. seems required, and sometimes such a dose does not entirely control symptoms and sedimentation rates. Perhaps small doses will be sufficient in cases in which the disease is mild.

**Additional Measures.**—Whatever analgesic agents, physical therapy, or other remedies were being administered, use of them was stopped several days to three weeks before compound E was employed. The factor of "hospitalization" (rest in bed, inadvertent "psychotherapy") was unavoidable, but except as they were disabled the patients were ambulatory and, when improved, were encouraged to assume as much activity as convenient, inside and outside the hospital, such as walking and shopping downtown. One patient, a local physician, eventually was given compound E as an out-patient after he returned to work.

## Clinical Effects of Compound E

**Initial Effects on Muscles and Joints.**—In each of the fourteen patients the initial results were as follows. Within a few days there was marked reduction of stiffness of muscles and joints, lessening of articular aching or pain on motion and tenderness, and significant improvement of articular and muscular function (Table). A pattern of improvement was evident. Usually the fibrositic component (muscular and articular stiffness) began to diminish first, often within the first forty-eight hours after use of the hormone was begun, and often was markedly or completely relieved within a few days. Second, articular tenderness and pain on motion were lessened. Then articular swellings generally diminished, sometimes fairly rapidly and completely, occasionally tardily and incompletely (perhaps a matter of dosage). In three cases mild flexion deformities of knees or elbows disappeared within seven to ten days. In another patient (Case 6) a knee, flexed at 165°, straightened to 175° after the use of compound E for ten days, flexed again to 150° when the control injections of cholesterol were being given, and later straightened to 180° when adrenocorticotrophic hormone was employed.

Those who had found the following manoeuvres difficult or impossible often were able within a few days to do them much more easily or even "normally": getting in or out of bed unassisted, rising from chairs or toilets, shaving, washing the hair or back of the neck, opening doors with one hand, wringing a wash cloth, lifting a cup or book with one hand, and climbing stairs.

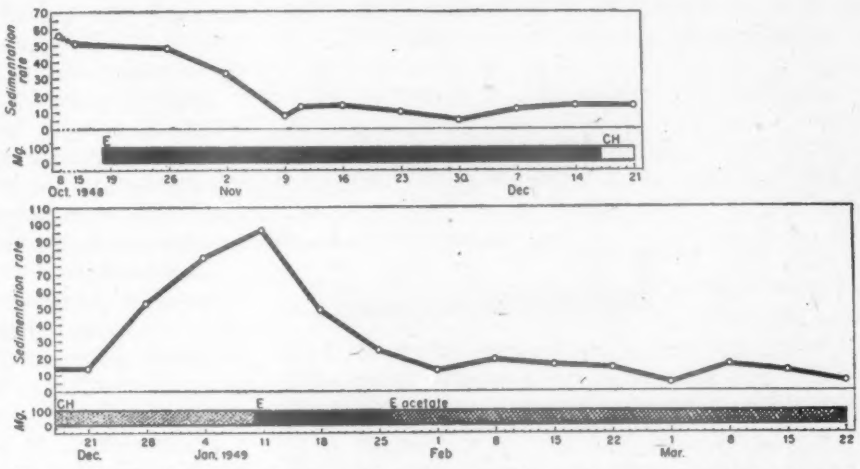


FIG. 1 (Case 3).—The effect on the sedimentation rate of compound E or E acetate, given for two separate periods to a 64-year-old man with severe rheumatoid arthritis of three years' duration. Note that the sedimentation rate rose when the control solution, CH (cholesterol), was substituted for compound E.

**Other Clinical Effects.**—The appetite often was rapidly improved. Several patients gained weight on routine diets; for example, 21·5 lb. in ten weeks; 17·5 lb. in two months; 19 lb. in forty days; 15 lb. in twenty-seven days; 7·5 lb. in twenty-six days. Improved strength was frequently noted. Several patients stressed the loss of the "toxicity" of the disease and experienced a marked sense of well-being. This euphoria apparently represented not mere relief from pain but a positive factor accompanied by increased mental capacity and activity, sometimes to the point of mild "comfortable" insomnia. We called the attention of our psychiatric colleagues to this euphoria and they are carrying out a series of observations on it.

**Effects when Short-term Administration was discontinued.**—Compound E was given to nine of our fourteen patients for only eighty to sixty-one days. Then, unknown to the patients, injection of the hormone was abruptly replaced by injection of the control preparation, cholesterol. In eight of the nine cases symptoms began to return or to increase promptly, generally within two to four days. The arthritis returned slowly in most cases, and rapidly in two. Sedimentation rates usually increased promptly, occasionally to more than was noted before the hormone was given (Table).

One patient, a farmer's wife, came in a wheel chair, improved markedly after injection of the hormone, and was soon walking well. Her sedimentation rate decreased 89 mm. (from 103 to 14 mm.) in thirty days (Case 7). Then the hormone was replaced by cholesterol. Although the sedimentation rate began to rise promptly (to 58 mm. eleven days after use of the hormone was stopped), she maintained practically all of her improvement for twenty-three more days in the hospital and for at least five weeks since returning to the farm and house work.

We hope that in other patients such relief will continue after injections are stopped more often than has occurred so far in our small series of patients with rather severe rheumatoid arthritis.

**Effect of Repeated or Prolonged Administration.**—Two patients (Cases 2 and 3) improved satisfactorily during eleven and eight weeks of injections, relapsed promptly but partially when the hormone was replaced by cholesterol for seventeen and twenty-four days, respectively, and again improved strikingly after use of the hormone was resumed in January. Each is now almost free from symptoms (Fig. 1).

A local physician (Case 4) was relieved by each of two periods of use of compound E and became worse in each interim. His sedimentation rates reacted appropriately. He said: "When I take the injection I lose completely my most distressing symptom, 'toxicity'; also all of my fibrositis and most but not all of my arthritis. All I have left is arthritis in miniature."

The hormone has been given daily, in varying doses, to one patient since Sept. 21, 1948, and to another since Dec. 24. In the latter case (Case 5) a daily dose of 100 mg. of compound E or E acetate has controlled symptoms completely for most, but not all, of the time. The patient occasionally has "arthritis in miniature" for a few days.

The condition of our first patient, described previously, has been the most difficult to control. Although her arthritis was effectively abated, it has never been completely relieved by continued daily doses of from 75 to 100 mg. of compound E or E acetate. Minor articular flare-ups have often occurred. Sometimes when the usual dose was employed, but especially when larger doses were utilized to control the flare-ups, interesting

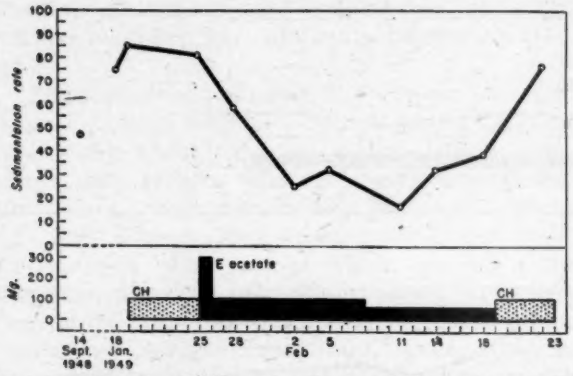


FIG. 2 (Case 9).—Effect of compound E acetate on the sedimentation rate of a 44-year-old woman with severe rheumatoid arthritis of two years' duration. Note that at first the sedimentation rate was not affected by the control solution, CH (cholesterol); then the rate decreased notably when an adequate dose of compound E acetate was used; then it increased when the dose of E acetate was reduced to 50 mg.; finally, when the use of compound E acetate was discontinued and cholesterol was substituted, the sedimentation rate increased markedly.

and important phenomena occurred. The patient would suddenly gain 4 to 7 lb. within two to four days, and then as suddenly lose the excess by way of spontaneous diuresis. There appeared some acne, mild hirsutism, and rounding of facial contour. Her menses, always irregular, ceased recently. In this one case prolonged use of the hormone presumably has induced a temporary endocrine disturbance which is being studied in the metabolic unit.

Much more experience is needed before we shall know how effective or safe the prolonged administration of compound E will be.

### Laboratory Effects of Compound E

**Sedimentation Rates.**—In every case, when compound E or its acetate was employed, sedimentation rates decreased markedly; sometimes promptly and rapidly, sometimes more slowly (Fig. 2). In a few cases the rate was refractory the first three to nine days, despite marked clinical improvement (Fig. 1). Sedimentation rates usually decreased at the "moderate speed" of 2 to 4 mm. daily average, in other cases "rapidly" at a daily average of 4 to 7 mm., occasionally at the "very rapid" rate of more than 7 mm. daily. Rates of decrease varied from patient to patient and from time to time in the same patient, and were influenced by the dose of our different preparations of compound E. Most rates became normal within ten to thirty-five days (Table), but rates, although much reduced, did not become normal in Cases 1, 2, and 14.

**Serum Proteins.**—When serum globulin was increased and albumin-globulin ratios were low or reversed, the use of compound E, if continued longer than a few days, lowered concentrations of globulin and normalized albumin-globulin ratios.

**17-Ketosteroids.***—Urinary concentrations, which usually were in the low normal range were reduced by the use of compound E, and thereafter were sometimes but not always reduced still more for a little while, then increased, but remained in the low normal and even subnormal range.

**Corticosteroids.***—The excretion of corticosteroids in the urine always increased when compound E was used. Usually there was a peak of a few milligrammes (not more than 5), which was followed by a decline to a fairly constant level between 1 and 2 mg.

**Haemoglobin.**—In four anaemic patients given the hormone for several weeks the haemoglobin increased 1·4, 1·8, 2, and 2 g. per 100 c.cm. In two others given the hormone for only ten to twenty days, values rose 0·5 and 1·4 g.

**Erythrocytes.**—In patients given the hormone more or less continuously, counts increased by 500,000 to 1,000,000 cells per cubic millimetre within a few weeks.

### Relation of Dose of Compound E to Effects

Generally, but not always, symptoms and sedimentation rates responded coincidentally. When rates were temporarily refractory, an increased dose (150 to 200 mg. daily) utilized for several days, as a rule caused rates to decrease. It has been somewhat "easier to control the patient than his chart". Obviously, doses must be individualized.

### Effects of Compound E on Synovial Disease

Articular biopsy has been carried out on four patients before, but thus far on only one of these same patients after, use of the hormone. The specimen of synovia removed from a knee forty-three days after injection of the hormone was begun was not normal, but histologically showed evidence of healing, and much less inflammation than did the specimen from the same knee beforehand.

### Toxicity and Overdosage of Compound E

Satisfactory criteria for the chemical and physical properties of compound E and its acetate have been established. But before this was accomplished the use of two early samples coincided with the occurrence of articular flare-ups, stuffiness of the ears, and mild dizziness. We observed no notable reactions of toxicity when later preparations of

* We are indebted to Dr. H. L. Mason of the Clinic for determination of the 17-ketosteroids and corticosteroids.

compound E or E acetate were used. Transient pain in the epigastrium developed in one patient. Use of the agent was stopped for four days, then continued for many days without recurrence of symptoms. Transient oedema, generally pretibial, has occurred occasionally. It disappeared, sometimes spontaneously, or when the dose of the hormone was reduced, or when potassium nitrate was employed orally. The effects of the hormone on electrolyte and water balance are being studied.

As stated previously, symptoms presumably related to overdosage occurred in one case in which the hormone was used continually since Sept. 21, 1948. Experiences with other types of hyperadrenalism lead us to believe that this condition is reversible.

**Use of Related Compounds in Rheumatoid Arthritis**

We are investigating the effects of related compounds, such as dehydrocorticosterone (compound A) (Mason and others, 1937), 17-hydroxycorticosterone (compound F)* (Mason and others, 1938 ; Richstein and Shoppee, 1943), desoxycorticosterone (DCA) (Steiger and Reichstein, 1937), certain adrenal cortical extracts, and pituitary adrenocorticotrophic hormone (ACTH).

**Effect of Pituitary Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis**

Two female patients with severe rheumatoid arthritis received 100 mg. of adrenocorticotrophic hormone intramuscularly for twelve days.† Results of metabolic studies will be reported separately. Marked clinical improvement essentially similar to that resulting from the use of compound E occurred promptly. Within a few days there was striking reduction of stiffness, pain on movement, and articular tenderness. Sedimentation rates decreased even more promptly and steadily than when compound E was employed : from 93 to 18 mm. within nine days in one case (Fig. 3) ; from 78 to 5 mm. within twelve days in the second case.

Side effects resulted from : (1) small amounts of posterior pituitary extracts with the adrenocorticotrophic hormone, and (2) the biochemical alterations induced by adrenocorticotrophic hormone. Noted were a sense of exhaustion, transient gas pains, heaviness in the chest and moderate elevation (20 to 40 mm.) of blood pressure.

There were alterations in blood and urine chlorides, in electrolytes and the carbon dioxide combining power of the blood, and in the excretion of 17-ketosteroids and corticosteroids in urine.

Both patients also received compound E either some time before or after the use of adrenocorticotrophic hormone. Relief from symptoms of arthritis was about the same when either hormone was employed ; when the use of either was discontinued the symptoms of arthritis and sedimentation rates quickly increased.

**Effect of Dehydrocorticosterone (Compound A)**

A woman with severe rheumatoid arthritis who later responded very well to compound E and to adrenocorticotrophic hormone was not benefited by the intramuscular use of 100 mg. of compound A daily for seven days. Two more patients are now receiving compound A.

**Rheumatoid Arthritis and Its Relationship to Certain (Other) Non-microbic Arthritides**

The syndrome of Addison's " disease " results whether the adrenal glands are impaired by atrophy, tuberculosis, or tumour. To what extent could rheumatoid arthritis be merely a syndrome produced by any factor which causes a deficiency of adrenal hormone ? Do some of the non-microbic arthritides usually considered " specific " (such as the arthritis of lupus erythematosus, of psoriasis, of chronic ulcerative colitis, or even of acute gout and rheumatic fever) represent likewise a transient deficiency of adrenal hormone, merely an " adrenal complication " of different parent-diseases, are some of these articular complications essentially identical with " rheumatoid arthritis " ?

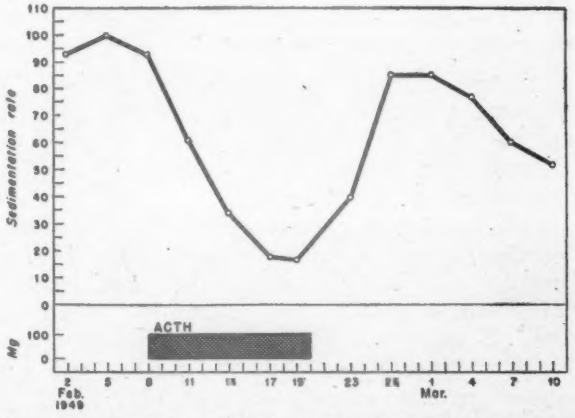


FIG. 3 (Case 14).—Effect of pituitary adrenocorticotrophic hormone (ACTH) on the sedimentation rate of a 45-year-old woman with moderately severe rheumatoid arthritis of five years' duration. The rate decreased markedly during the use of ACTH, then increased rapidly. Note the " rebound " between February 26 and March 10 ; thereafter the rate increased again.

* We are indebted to Dr. E. Gifford Upjohn of the Upjohn Company for the sample of 17-hydroxycorticosterone (compound F).

† We are indebted to Armour and Company, and particularly to Dr. John R. Mote, director of medical research for that company, for supplies of this pituitary hormone.

### Application of the Use of Adrenal and Pituitary Hormone to Conditions other than Rheumatoid Arthritis

With the aforementioned conjectures in mind, we are giving compound E to a patient with severe lupus erythematosus and polyarthritis and to another with acute rheumatic fever. The encouraging results will be reported later.

Listed elsewhere (Hench, 1949) were several conditions usually relieved by jaundice or pregnancy or both. The mechanism of relief may become less mysterious if some of these conditions are found to be responsive to compound E, and others to adrenocorticothrophic hormone, which of course stimulates the production of not one but several adrenal hormones. A patient who had myasthenia gravis, treated at the Mayo Clinic by Eaton and Sprague (unpublished data), was unrelieved by the daily use of 100 mg. of compound E for twelve days, but a patient with this disease treated elsewhere was relieved by adrenocorticotrophic hormone (Soffer and others, 1948). The inference is obvious.

It is of course most unfortunate that the available amounts of compound E and of adrenocorticotrophic hormone are so small and may remain so for months to come. The production of compound E by partial synthesis is being expanded; total synthesis may be an eventuality. The supply of adrenocorticotrophic hormone, a complex protein, depends on the availability of pituitary glands. Opportunities to enlarge the scope of these investigations in the near future appear to depend on improvements in the production of compound E.

### Conclusions

Certain clinical and biochemical features of rheumatoid arthritis have been markedly improved by the daily intramuscular injection of either the adrenal cortical hormone, 17-hydroxy-11-dehydrocorticosterone (compound E), or the pituitary adrenocorticotrophic hormone, ACTH. Articular, muscular, and other symptoms were lessened notably, and sedimentation rates were reduced when either hormone was employed; when the use of them was discontinued symptoms and signs of rheumatoid arthritis usually, but not always, returned or increased promptly.

Certain clinical facts and theoretic considerations combine to suggest that these adrenal and pituitary hormones may be useful against other rheumatic diseases and against certain non-rheumatic conditions which are generally relieved by pregnancy or jaundice.

### References


Barsi, I. (1947). *Brit. med. J.*, **2**, 252.
Eaton, L. M., and Sprague, R. G. Unpublished data.
Gardner, Frances, Stewart, Alice, and MacCallum, F. O. (1945). *Brit. med. J.*, **2**, 677.
Hanssen, P. (1942). *Acta med. scand.*, **109**, 494.
Hench, P. S. (1933). *Proc. Mayo Clin.*, **8**, 430.
—— (1934). *Ann. intern. Med.*, **7**, 1278.
—— (1935). *Med. Clin. N. Amer.*, **19**, 573.
—— (1938a). *Proc. Mayo Clin.*, **13**, 161.
—— (1938b). *Arch. intern. Med.*, **61**, 451.
—— (1938c). *Brit. med. J.*, **2**, 394.
—— (1940). *Med. Clin. N. Amer.*, **24**, 1209.
—— (1949). *Proc. Mayo Clin.*, **24**, 167.
MacCallum, F. O., and Bradley, W. H. (1944). *Lancet*, **2**, 228.
Mason, H. L., Hoehn, W. M., and Kendall, E. C. (1938). *J. biol. Chem.*, **124**, 459.
——, ——, McKenzie, B. F., and Kendall, E. C. (1937). *Ibid.*, **120**, 719.
Reichstein, T., and Shoppee, C. W. (1943). "The Hormones of the Adrenal Cortex." In Harris, R. S., and Thimann, K. V.: "Vitamins and Hormones," Vol. 1. Academic Press, Inc., New York.
Rennie, J. B., and Fraser, T. N. (1946). *Glasgow med. J.*, **27**, 157.
Soffer, I. J., Gabrilove, J. L., Laqueur, H. P., Volterra, M., Jacobs, M. D., and Sussman, M. L. (1948). *J. Mt Sinai Hosp., N.Y.*, **15**, 73.
Sprague, R. G., Power, M. H., Mason, H. L., and Cluxton, H. E. (unpublished data). "Metabolic Effects of Synthetic Compound E (17-hydroxy-11-dehydrocorticosterone) in 2 Patients with Addison's Disease and in 1 with Coexisting Addison's Disease and Diabetes Mellitus."
Steiger, M., and Reichstein, T. (1937). *Helv. chim. Acta*, **20**, 1164.
Thompson, H. E., and Wyatt, B. L. (1938). *Arch. intern. Med.*, **61**, 481.


### Effet de l'Hormone Corticale de la Surrénale (17-Hydroxy-11-Dehydrocorticostérone : Composé E) et de l'Hormone Pituitaire Adrénocorticotrophique sur l'Arthrite Rhumatismale


#### Conclusions

Des injections intramusculaires de l'hormone corticale de la surrénale, 17-hydroxy-11-dehydrocorticostérone (composé E) ou de l'hormone pituitaire adrénocorticotrophique, ACTH, ont amené une amélioration notable de certains caractères cliniques et biochimiques de l'arthrite rhumatismale. Les symptomes articulaires, musculaires, et autres ont accusé une regression marquée et le taux de la sédimentation globulaire a baissé, les deux hormones agissant séparement d'une façon similaire. Généralement, mais pas toujours, l'interruption du traitement était rapidement suivie du retour ou de l'accentuation des signes et des symptomes de l'arthrite rhumatismale.

L'ensemble de certains faits cliniques et des considérations théoriques semble montrer que ces hormones, la corticale et la pituitaire, peuvent être utiles contre d'autres affections rhumatismales et contre certaines affections non rhumatismales, susceptibles d'etre soulagées par une grossesse ou par un ictère.

# DRUGS IN THE TREATMENT OF RHEUMATIC DISORDERS

BY

N. MUTCH

Drugs are important in the treatment of rheumatic diseases, but the role they play is essentially a contributory one, to be fitted carefully into the general therapeutic plan. Their greatest uses are to be found in acute rheumatic fever and its clinical variants, in gout, non-articular fibrositis, and those forms of chronic arthritis, typified by rheumatoid arthritis, in which intermittently progressive inflammatory lesions are produced in joints which have become subtly potentiated or in joints which have been involved during acute bacterial infections. The group includes joints in which the lesions of chronic inflammation are modified by those of coincident growth, senescence trauma, osteo-arthritis, and gout.

### Rheumatic Fever

Salicylates, used since 1876, maintain the foremost place in the treatment of this disease. Their striking clinical effects still lack pharmacological explanation. Rheumatic pain is thought to be caused by local exudates which arise from capillary damage produced by histamine. Swyer (1948) has shown that the wheal which follows the intradermal injection of histamine does not form in subjects taking salicylates, and has so provided some evidence that salicylates may act by antagonizing the effects of local histamine-release near the joints. Hyaluronidase also is suspected of being concerned in the production of rheumatic effusions. The ferment is present in many tissues and in haemolytic streptococci. It hydrolyses hyaluronic acid and promotes the diffusion of bacteria and their products through connective tissues. Experimentally when injected intradermally with Evans Blue it causes rapid dispersal of the latter. Guerra and Gil (1946, 1947) found by this test that rheumatic fever patients are particularly sensitive to hyaluronidase and that the reaction could be prevented by the prior administration of salicylates. Swyer could not confirm this latter observation and suggested the Guerra's solutions might have been contaminated with histamine. The idea, however, still remains plausible that the rapidly formed effusions of acute rheumatic fever result from the combined effects of capillary damage by histamine and the diffusion of toxins by hyaluronidase, and that salicylates give clinical relief by inhibiting the effects of the former process. Whilst there is universal agreement that salicylates reduce the fever, joint swelling, and pain of rheumatic fever, it still remains uncertain how far the drug can eradicate the disease itself or even benefit the rheumatic heart. After much research their claim to act as true chemotherapeutic agents remains unproven. Salicylic acid is *o*-hydroxybenzoic acid. Its *m*- and *p*-isomers are therapeutically inactive; but gentisic acid, which is 2,5,-dehydroxybenzoic acid has some influence over acute rheumatic fever. Meyer and Ragan (1948) consider its sodium salt to be as effective as sodium salicylate in this condition and see a mutual relationship between the clinical effect of sodium gentisate and its inhibitory action *in vitro* on the diffusing factor.

**Sodium Salicylate.**—Modern methods of analysis now enable clinical phenomena to be more accurately correlated with salicylate concentrations in the blood. Sodium salicylate taken by mouth is quickly absorbed and attains a peak concentration in the plasma after two hours. To prevent any dip in the graph of successive plasma concentrations the dosage interval must not be greater than two hours. Elimination takes place much more slowly than absorption, and on a two-hourly dosage scheme cumulation occurs so that the plasma concentration curve shows a steady rise instead of the desired plateau. If large individual doses are repeated, toxic symptoms will inevitably arise. Their onset should be carefully noted and the dose adjusted. Some salicylism always occurs before the full therapeutic effect on joints and fever has been attained, but in chemotherapeutic tests higher degrees of intoxication have been induced, bordering on the fatal. One of the earliest warning symptoms is hyperpnoea resembling that of diabetic acidosis. More serious still are delirium and coma. Bowen and others (1936) reported that often the $CO_2$-carrying power of the blood is not materially affected. Gebert (1931) found that *p*H values might indeed sometimes be raised so that the administration of alkalis cannot be expected entirely to alleviate the condition.

Coburn (1943) was the first to publish controlled

observations on massive salicylate therapy, and he stated that plasma levels of 35 mg. of salicylate per 100 ml. were sufficient to suppress infection, shorten the period of illness, decrease the relapse rate, and prevent serious heart involvement. Warren and others (1946) found that in young adults a daily dose of 7 g. to 8 g. was required to establish such concentrations. Manchester (1946) confirmed Coburn's findings. He injected a litre of 1 per cent. sodium salicylate solution intravenously each day for four to ten days, after which 10 g. daily combined with 8 g. of sodium bicarbonate were given by mouth on a four-hourly plan. Reid (1948) thought that some curative effect could be seen in his small series of twelve patients in whom he secured plasma salicylate levels of 20 mg. to 46 mg. per 100 ml.

The severe degree of poisoning frequently induced by such technique would be justified if there were full assurance that the incidence of cardiac lesions could indeed be reduced, but other observers have not been so fortunate. Warren and others (1946), using graded dosage schemes (1) 2 g. to 7 g. daily, (2) 10 g. to 16 g. daily, (3) 1 litre 1 per cent. sodium salicylate in normal saline intravenously each day for a week followed by 10 g. to 16 g. daily by mouth, failed to find any advantage in intravenous therapy. In their hands even the largest doses did not prevent the onset of heart lesions or abate the severity of lesions already established, with the possible exception of pericarditis. Harris (1947) likewise failed to find that massive doses of salicylates (13 g. to 19·5 g. daily) in any way benefited patients with active rheumatic carditis. It would appear that as yet there is no proven advantage in modifying the traditional routine of allowing the relief of pains and swellings in the joints to be the criterion of adequate dosage, the patient being expected to submit to the discomforts of mild salicylism, but not to the major risks of intoxication or intolerance.

**Substitutes for Sodium Salicylate.**—Hypersusceptibility and idiosyncrasy sometimes interfere with the administration of sodium salicylate. Related compounds can then be given, such as acetyl-salicylic acid, salicin, or the carbonate of ethyl salicylate (Sal-ethyl Carbonate), a non-irritant tasteless powder of low solubility (dose: 0·3 g. to 1 g. at intervals of two to three hours).

*Acetyl-Salicylic Acid.*—Although acetyl-salicylic acid contains a lower percentage of the salicylate radicle than sodium salicylate does, its anti-rheumatic activity is about three times as great as that of the parent salt and its toxicity is even less than might have been inferred from its salicylate content. The risks of producing toxic symptoms with clinically effective doses are therefore less. Its special disadvantages arise from idiosyncrasy and gastric irritation. The usual expressions of the former are urticaria, oedema, and a very resistant form of asthma, which preclude further use of the drug. Gastric irritation can be prevented to a large extent by dissolving the compound in a solution of potassium citrate and so reducing the contact-concentration at the mucosal surface.

The sodium, lithium, and calcium salts are soluble and in solution are better tolerated than the acid itself, but they too are irritant if swallowed in tablet form. In aqueous solution they quickly decompose, and under ordinary pharmaceutical storage conditions they break down slowly even in their solid form to mixtures of the salts and free acids of salicylic, acetic, and acetyl-salicylic radicles, which are far more irritant than acetyl-salicylic acid itself. The stability of the calcium salt can be increased by incorporating with it a small proportion of calcium chloride. Calcium acetyl-salicylate stabilized in this way (Mutch, 1934) can be kept for several weeks in its solid form, but not in aqueous solution. Even acetyl-salicylic acid decomposes slowly in its solid form, especially if atmospheric moisture is not carefully excluded, and it should be used whilst still fresh from the manufacturer's plant. If when a bottle of tablets is opened an odour of acetic acid is detected, the contents should be viewed with suspicion. Perhaps the safest method is to use the simple acetyl-salicylic acid dissolved in an excess of sodium bicarbonate solution. All acids present are then converted into innocuous sodium salts and the excess of alkali, by neutralizing the gastric juice, hinders the release of the free acids in the stomach. Such solutions, however, cannot be kept and must be prepared freshly every day.

*p-Aminobenzoic Acid.*—This substance increases the clinical effect of salicylates and in heavy dosage (3 g. to 5 g. two- to three-hourly) has some direct influence on the joint manifestations of rheumatic fever (Rosenblum and Fraser, 1947). Its chief action, however, is to diminish the rate of salicylate excretion by the kidneys and so raise the salicylate level in the blood (Dry and others, 1946 ; Bélisle, 1948). For this purpose 2 g. are given two-hourly. It is absorbed and excreted rapidly but, since its chief anti-rheumatic action is exerted indirectly by a raising of the plasma salicyl titre, it is unlikely to prove of much value in diminishing the severity of toxic manifestations occurring during intensive salicylate therapy or caused by hypersusceptibility.

*Cinchophen.*—Introduced into clinical use in 1908, cinchophen had already been synthesized at

a much earlier date in 1887, and it shares with the so-called coal-tar antipyretics the distinction of being one of the earliest gifts of organic chemistry to therapeutics. Its effect on the rheumatic fever syndrome closely parallels that of salicylates. Even its dosage is similar, at 0·3 g. to 1 g. every few hours, but it does not attain a peak concentration in the blood quite so quickly and doses can be spaced at three- or four-hourly intervals. It may irritate the stomach, and has been known on rare occasions to produce angioneurotic oedema and symptoms resembling salicylism, but patients intolerant to sodium salicylate can usually take it without distress. It should be reserved for cases of extreme salicylate idiosyncrasy because its use is not entirely free from danger. It has long been known that it may cause a very fatal form of hepatitis, the incidence of which is not determined by the magnitude of the dose, the length of the course already taken, or any previous use of the drug. It remains unpredictable, and predisposition cannot be ascertained by any known test. During the period 1925 to 1936 a yearly average of about twenty cases of this type were reported in America, where the estimated annual consumption of the drug was at one time 90,000 lb. (White, 1931). The incidence was therefore about one case per 4,500 lb. consumed, and the death rate approximately one per 9,000 lb. From an analysis of the cases reported in the literature from 1913 to 1933, Snyder and others (1935) took an even less serious view of the risks and concluded that one death was attributable for every 17 million doses of 7½ gr. The danger attaching to its use in any individual is far less than any known surgical risk or that involved in chrysotherapy, and it can legitimately be employed when serious matters of life and health are at stake. It had been hoped that related compounds would be free from the stigma, but hepatitis has been reported after the use of the methyl ester (Novatophan), the allyl ester (Atoquinol), and neo-cinchophen, in which a methyl group is added to one of the benzene rings.

*Amidopyrine.*—The pain, pyrexia, and joint swellings of rheumatic fever respond to this drug also. The dose required (0·3 g. to 0·6 g. four-hourly) is comparable with that of sodium salicylate. On the rare occasions on which it is employed, it is customary to reduce the dose to 5 g. daily after the first twenty-four hours. Unlike the drugs already mentioned it does not irritate the stomach, but it has the grave disadvantage of occasionally causing agranulocytosis, from which deaths have occurred. Quantitatively the risk involved is far less than the risk of inducing hepatitis with cinchophen. Dameshek and Colmes (1936) showed that after incubation with a susceptible patient's blood, as small a dose as 10 mg. of amidopyrine injected intradermally into the same patient would cause an abrupt and severe leucopenia, but no clinically applicable test for predisposition has so far been devised and its occurrence remains unpredictable.

*Sulphonamides.*—Salazopyrin, a compound of sulphapyridine and salicylic acid, has recently been used in Norway (Svartz, 1948) in acute and chronic polyarthritis including cases of typical acute rheumatic fever, but without unequivocal success. Simple sulphonamides and penicillin have both proved powerless to give symptomatic relief or to check the course of the disease, but some evidence has been presented that sulphonamides may diminish the relapse rate. Coburn and Moore (1939) found that sulphanilamide given to rheumatic subjects after the onset of an interval attack of acute streptococcal infection of the throat did not protect them from recrudescence of rheumatic fever. Used prophylactically, however, it seemed to diminish the incidence of acute streptococcal throats and so was deemed indirectly to safeguard the users against recurrence of rheumatic trouble. Thomas and France (1939) used sulphanilamide in the same way during the winter months to protect rheumatic heart cases. Stokes (1947), using 0·5 g. to 1·5 g. daily for children, could not find any decrease in the haemolytic-streptococcus-carrier rate and reported a significant rise in the proportion of sulphanilamide-resistant organisms in the throat. Griffith (1947) found that sulphathiazole and sulphadiazine used systematically throughout the year reduced the frequency of acute streptococcal infections of the throat, and surmised that in any given group of people who had already had an attack of rheumatic fever this routine might reduce their liability to further attacks. Clearly there is insufficient evidence on the point to justify the systematic dosing of patients with drugs possessing such harmful potentialities.

## Gout

The intrinsic nature of this disorder being still obscure, treatment remains empirical and intuitive.

**Acute Gout.**—Colchicum, in use since the sixteenth century, is still employed for the acute attack. Most patients obtain dramatic relief although some fail entirely to respond. The active agent is the alkaloid colchicine, and medication can be carried out either with colchicine, 0·5 mg., or vinum colchici, 1 ml. every two or three hours for four or five doses and then at somewhat longer intervals until relief is obtained or nausea, diarrhoea, or other toxic symptoms manifest themselves. Opium can be used judiciously to counteract excessive looseness

of the bowels, but it is undesirable to induce a state of constipation. Colchicine is cumulative and very poisonous. A total intake of 8 mg. should not be exceeded lightly. With overdosage, colic, haematuria, oliguria, and, later, ascending paralysis of the nerve stem may occur. Its action is curiously specific and no relief is afforded to other types of pain or inflammation. It does not affect the excretion of uric acid or the concentration of urates in the blood. Sodium salicylate and acetyl-salicylic acid are often used in conjunction with colchicine and for patients who fail to respond to it. They lessen the pain and inflammation around the joints and have the additional possible advantage of increasing the urinary output of uric acid and lowering its concentration in the blood. This result used to be acclaimed as conferring great benefit on the gouty patient, but it is now realized that the inference may not be justified, the old concept of an attack of gout as representing the deposit of biurate crystals from a supersaturated solution being no longer held adequate to explain the phenomena.

Cinchophen can also be used to relieve the pain, 0·5 g. every two hours for six or more doses.

**Chronic Gout.**—In this condition colchicine fails to give either relief or protection from recurrent outbreaks, and the drugs in widest use are the cinchophens and salicylates. Both groups relieve the pain of the gouty joint just as effectively as that of rheumatic fever, and both increase the excretion of uric acid whilst lowering its titre in the blood. In this respect cinchophen is the more effective and appears to act by lowering the renal threshold to urates. The modifications in purine metabolism and elimination induced by salicylates have not been so clearly analysed. In the absence of disease in the liver, kidney, and blood vessels, cinchophen can be taken for three or four days in each week in doses of 0·5 g. to 1·5 g. daily until the concentration of urates in the blood becomes normal. This routine has often been kept up for many consecutive months or even years without disaster. Cinchophen is irritant and has been used experimentally to produce gastric ulceration. Similar lesions have been attributed to its use in man (Bloch and Rosenberg, 1934 ; MacBryde, 1940). Sodium bicarbonate can be given to afford some protection to the stomach and to supplement the citrates, acetates, and bicarbonates of sodium, potassium, and lithium commonly given to render the urine alkaline and keep the extra urates in solution. Biurates are less soluble than the more acidic quadriurates, but none the less urates dissolve more freely in an alkaline urine than in an acid one provided that the alkalinity is not due to the presence of free ammonia. Lysidine, piperazine, hexamine, and thyminic acid have been used traditionally for the same purpose and in spite of much adverse criticism are still greatly in vogue, especially in France. Although vagaries of urate excretion in gout have received so much attention, it must be confessed that cinchophen may give clinical relief without reducing the concentration of urates in the blood and that it may reduce these urates satisfactorily without controlling the clinical condition. Nevertheless, the great relief which it usually gives to the sufferer from chronic gout is acknowledged everywhere.

As an alternative, generous doses of sodium salicylate or acetyl-salicylic acid can be used, 7 g. daily of the former or 4 g. of the latter, together with protective alkalis. A fall in the urate content of the blood usually follows, but the value rises again when medication comes to an end. To secure results of sufficient permanency the course of treatment should be kept up for three or four weeks.

### The Rheumatoid Group

Many nostrums have been employed in these conditions, but first consideration must be given to those methods which are based on modern concepts of pathogenesis. They are designed to protect the joints from noxious substances of microbic and other origins present in the blood and to promote the healthy activity of all vital functions depressed by abnormal circumstances of the patient's habits and environment; the impairment of his locomotor powers and his confinement to chair, bed, house, or clinic. There are also putative chemotherapeutic agents for the destruction of hypothetical causal organisms. Experience has shown that this considerable equipment can be deployed greatly to the advantage of most patients if discrimination is exercised in selecting the remedial units and in applying them in their appropriate contexts and sequences. Although the primary cause of rheumatoid arthritis remains obscure, much is known about those perpetuating factors which determine the chronicity of the local inflammatory process and the rate of structural disintegration. In the case of a tubercular joint the chief perpetuating factors are movement and mechanical stress. Provided that the general level of health is maintained and the primary focus is not one of advancing type, the arthritic lesion responds satisfactorily when the joint is immobilized and its internal surfaces freed from compression. The rheumatic joint differs from the tubercular in that it appears to be much more vulnerable to abnormal blood constituents which provoke inflammatory

reactions of varying intensity. The nature of these substances and their modes of action remain matters for enquiry. They may be antigens initiating intracellular antibody reactions or other bacterial products exciting Arthus' phenomena or substances of hitherto unknown type. They are not necessarily related directly to the elusive primary cause. For example, the eating of certain foods or the drinking of particular wines may be followed by strong inflammatory responses in typical rheumatoid joints.

The septic focus has long been held to be an important generating point of such provocatives and little success can be expected from medicinal treatment unless all surface areas of gross infection have been effectively cleansed by dental and surgical procedure. Attention can then be focused on the digestive tract, where provocatives might gain access to the blood from inflamed organs, for example the appendix or gall bladder, from polypi and other tumours, from microbic infestation of the mucosa, and from the bowel contents themselves. The last group is the one with which the present discussion is concerned. Arthus has shown that his reactions can be excited by combinations of extracts from widely dissimilar organisms. Thus the local injection of the filtrate from one bacterial culture followed at a correct interval of time by the intravenous injection of the filtrate from an entirely different species of bacterium may lead to an intense local disturbance at the first injection site. It does not seem unlikely, therefore, that reactions might be produced in a given rheumatoid joint by different provocatives on different occasions. Consequently all suspected areas should be purified.

The study of allergy and of the formation of antibodies and precipitins after the ingestion of foreign proteins and vaccines has revealed that molecules of sufficient complexity to retain antigenic properties can pass through the intact lining of the bowel. The normal products of digestion appear to be innocuous, except to those subject to food allergy. The chief responsibility for the production of pathogenic compounds must be placed on the activity of micro-organisms. All deviations of digestion should, therefore, be corrected and opportunities reduced for the production and absorption of antigens and other provocative compounds thrown off by the intestinal flora or arising from the action of digestive enzymes operating in a bacterially contaminated medium. In the small intestine zymolysis should proceed under aseptic conditions, but in many circumstances bacteria reach the area from inflamed zones above, whilst others may ascend from below, and a third quota be shed from the adjacent mucosa whenever it is infected. The large intestine always contains bacteria of many races which have established what may indeed be a helpful symbiosis, but microbic activity of abnormal form and degree will develop if an excess of nutrient matter is allowed to mix with the faeces. This occurs whenever diet is excessive or unsuitable or the power of the digestive enzymes is impaired or the processes of absorption are faulty. The diet must be simple and correctly balanced. Evacuation must be satisfactory. These are the primary essentials of alimentary therapeutics, but cannot be dealt with in detail here. Colonic lavage often relieves rheumatic pain in the severely constipated and can be used to introduce potassium permanganate, lactic acid, or other substances to cleanse such remnants as cannot be washed away. Ox bile will reduce the surface tension of the lavage fluid and facilitate its penetration of recesses, ledges, and diverticula.

**Digestants.**—Acids and antacids have their uses but there are more direct methods of assisting the digestive juices. Many pharmaceutical enzyme preparations are too weak to make any material difference to gastro-intestinal chemistry in the doses which are prescribed. Two, however, appear to satisfy the quantitative requirements.

*Takadiastase*, produced by the action of aspergillus oryzae on moist rice, is used to convert starch into sugar in the manufacture of saké and some forms of whisky. Good samples are six times as powerful as malt-diastase and outclass even diastase vera. Most diastatic ferments are destroyed by the acid in the stomach, but takadiastase passes through without impairment. In amylaceous dyspepsia 200 mg. or 300 mg. doses at meal times produce obvious clinical improvement. When an excess of carbohydrate is retained in the colon, the streptococcal elements in the flora gain dominance over the coliform organisms. If stagnation is profound, they in their turn succumb to the advancing acidity generated by the acidophilus group, but more usually the process continues only as far as the streptococcal stage. It can be argued that a flora of this type is harmful to the rheumatic subject, and indeed it is often associated with an increase in rheumatic pain. It can be corrected by simplifying and reducing the starchy foods in the diet, treating the constipation, and giving takadiastase to augment the natural diastase of the pancreatic juice.

*Erepsin.*—The proteolytic enzymes secreted by the intestinal mucosa are collectively called erepsin and complete the proteolysis initiated by the secretions of the pancreas and stomach. The work

of Renshaw (1947) encourages the belief that erepsin can be made to play a useful part in anti-rheumatic therapy. Its action is to speed the later phases of protein digestion and so reduce the amount and complexity of the protein remnants which reach the infected areas of the lower bowel. It is available as Benecol, an extract of intestinal mucosa in the form of tablets specially coated to prevent inactivation by the gastric juice. Three to nine tablets are taken daily between meals.

*Bile Salts.*—Although devoid of enzyme activity, bile salts are essential to the digestion of fats. They increase the flow of bile, activate the lipase of pancreatic juice, confer water solubility on fatty compounds, and promote the formation of superfine emulsions essential for full lipolysis and absorption. They can be prescribed as sodium tauro-glycocholate B.P.C. in 250 mg. doses between meals. Being hygroscopic, soluble, and in high concentrations irritant to the gullet, they must be given a suitable protective coating. They effectively control the symptoms of minor fat intolerance and true biliousness. A small marginal dose to supplement the bile salts produced naturally in the liver is all that is needed in most cases, and since they are absorbed and re-excreted in the bile over and over again they need not be given every day. Three or four doses weekly usually suffice. Alternatively dehydrocholic acid and sodium desoxycholate can be used for the same purpose as therapeutic equivalents, although the former lacks the valuable direct action on lipolysis possessed by the natural bile salts.

**Intestinal Antiseptics.**—The older remedies of this type have long been discredited. Sulphaguanidine, succinyl-sulphathiazole, and phthalyl-sulphathiazole now enable big reductions to be made in the colonic flora, but their applications in rheumatic diseases are very limited. Their administration is not followed by any obvious change in the condition of the joints, but the general condition of a bed-ridden patient with toxaemia resulting from grossly dislocated digestion may be temporarily improved. For more continuous use less toxic compounds are required. Those which seem to have proved most satisfactory are the halogen-substituted phenols.

Many have been studied, and germicidal power has been found to increase as more and more halogen atoms are introduced into the ring. Iodine has proved to be rather superior to bromine, and the bromine compounds are a little more active than those containing chlorine. Halogen derivatives of the higher homologues of phenol are more potent still, those containing the n-amyl group being strongest. The toxicity of most of them is low (Klarmann and others, 1934). The minimum lethal dose of p-chlorophenol injected subcutaneously into mice was estimated as 0·6 mg. per g. of body weight (Meleney and others, 1946). On the basis of body weight equivalence this corresponds to a 40 g. dose for an average man. A juster assessment was made by Gersdorff and Smith (1940), who compared the toxicities of o-, m- and p-chlorophenol using phenol as a control. In each case the toxicity of the chlorine compound slightly exceeded that of phenol. Pentachlorophenol is an exception, and although not very harmful in single doses, after repeated administration it acts as a cumulative poison. Most of the series dissolve freely in lipoid solvents but all except the simplest members are relatively insoluble in water; thus, p-chlorometaxylenol B.P., with a Riedel Walker coefficient of 36, dissolves at 1 in 3,000, 2.4.dichlorophenol, R.W. Coef. 13·3, is soluble 1 in 250, whilst o-chlorophenol is soluble 1 in 140 but its R.W. Coef. is only 2·3. The irritant and local analgesic properties of these compounds must also be taken into account.

Some of those in medical use are: parachlorometacresol B.P. and parachlorometaxylenol as external disinfectants. Tribromophenol, almost insoluble in water, is used in pill form (30 mg. to 120 mg.) as an intestinal antiseptic, p-chlorophenol (0·25 per cent.) for wounds, and the mixture known as T.C.P. (principally 2.4.dichlorophenol together with o- and p-chlorophenol) for external and internal purposes. In the last preparation a useful balance has been struck between solubility, potency, and irritancy and a 0·6 per cent. solution of mixed chlorinated phenols has been provided with germicidal power approximately equivalent to 10 per cent. aqueous phenol. After moderate dilution it is well tolerated by mouth and can be taken regularly for many months without any adverse effects.

Phenolic preparations not containing halogen substituents also have been used internally, for example, amyl-metacresol, R. W. Coef. 250 but almost insoluble in water. It is given in capsules containing 150 mg. dissolved in oil. Dimol "43", R.W. Coef. 43, is a mixture of alkyl substituted phenols and methoxyphenols employed for the same purpose. These substances, potent but insoluble, probably exert a little antibacterial action at all levels of the alimentary canal but do not greatly change either the faecal flora or the essential rheumatic syndrome. An aqueous solution of greater molecular strength of the simpler chlorinated phenols is far more effective clinically even though the constituent substances are less powerful germicides. Their absorption is rapid, so that their activity is probably expended in the small intestine. Even pentachlorophenol quickly finds its way into the circulation and Machle and others (1943) found peak values of 10 mg. per 100 ml. in rabbits' blood three hours after large but sublethal doses had been given by mouth. If taken some hours after the last meal of the day, solutions of mono- and dichlorophenols probably maintain bacteriostatic concentrations in the small intestine for a time and so protect the processes of normal enzymic digestion from chemical distortion by collateral microbic action. The diminution

in rheumatic pain which can follow such medication is often so striking as to suggest that some additional mechanism may be at work, such as the denaturing of abnormal breakdown products with harmful antigenic properties by their linkage with the administered drug.

**Mineral Adsorbents.**—If provocative substances entering or formed in the digestive tract could be destroyed, precipitated, or removed from aqueous solution in some other way, they would be prevented from reaching the circulation. Kaolin and other actively adsorbent materials are given with this objective in view. When more than one substance is taken up by an adsorbent, they may be modified by mutual interaction under the catalytic conditions obtaining at the adsorbing surface. In their original or modified forms they may be held firmly and excreted in the faeces, or in the new chemical environments encountered at lower levels they may be eluted or displaced by other compounds and so returned to solution. Whether after these vicissitudes they now reach the blood stream or not will be determined by the absorptive powers of the mucosa at the new alimentary level. In the face of so many factors the only method of assessing the practical value of mineral adsorbents in any particular disease is that of clinical trial. The two which have appeared to give most relief in rheumatic disorders are kaolin and acid-resistant alumina, but silica-gel, bentonite, and other strongly adsorbent materials might be tried.

Kaolin should be as pure as possible, for example kaolinum leve B.P., and since it tends to cause constipation it should be combined with an aperient. A useful combination is kaolin 10 g. in 250 ml. 0·5 per cent. aqueous sodium bicarbonate containing a sufficiency of Glauber's salts (magnesium sulphate is less suitable for this purpose) about half an hour before breakfast. The lining of the stomach and small intestine is thus washed over with the adsorbent whose residual activity is expended in the colon. A similar dose given at bed time, with a vegetable aperient substituted for the saline, will exert its action amongst the still digesting elements of the meals of the current day. Acid-resistant alumina (Mutch, 1946) should be selected for its adsorption potency and its freedom from antacid activity. If the usual acid-reactive gels used in the treatment of peptic ulceration are employed they will interfere with gastric digestion by lowering the acidity in the stomach and by destroying the pepsin (Schiffrin and Komarov, 1941). Alumina can be given as a supplement to kaolin since it adsorbs an entirely different range of compounds. Although somewhat catholic in its affinities, preferentially it takes up substances with anionic properties whilst kaolin selects the kationic.

**Upper Alimentary Lubrication.**—Many of the discomforts of dyspepsia (heartburn, eructations, repetitions, anorexia, nausea, vomiting and distension) resemble in minor form the syndrome of obstruction and can often be corrected by lubrication. For this purpose a 25 per cent. to 30 per cent. O/W emulsion of well homogenized heavy mineral oil answers well, since it mixes evenly with whatever fluids it may encounter and so sustains an even action. To exert the greatest effect on the pylorus, duodenum, and ileum, it should be given about twenty minutes before each meal so that it can find its way to all levels undiluted by the food. An even better clinical effect is produced if one of the adsorbents just discussed is suitably suspended in the continuous aqueous phase of the emulsion. Such preprandial dressing by adsorbent and lubricant in readily dispersible form is a measure of wide applicability for rheumatoid patients who are confined to bed and for others with persistent symptoms of the simpler forms of dyspepsia.

Before considering more specific measures it can be pointed out that the methods so far discussed for use in arthritic cases are just as useful in the treatment of the commoner forms of non-articular fibrositis. Some patients with the latter complaint are extremely sensitive to events in their alimentary tracts. The gastric delay caused by the persistent use of phenobarbitone is sometimes sufficient to perpetuate rheumatic pains of this type and even to cause relapse in a patient whose pains have previously been controlled.

**Septic Foci.**—The eradication of the septic focus is chiefly a surgical responsibility, but extensive infection of a chronic kind often persists in the throat, nose, and sinuses after all operative advantages have been taken. Bacterial insemination of the alimentary tract from such areas continues and can only be diminished by non-surgical means. Perhaps the best method of dealing directly with these infected areas is to use nebulized mists of penicillin and sulphonamide. Hand nebulizers are inadequate. To disperse a sufficiency of drug in an appropriately fine form the higher power and capacity of apparatus operated by oxygen pressure or by an electrically driven compressor are needed. It has been shown (Mutch, 1944 ; Mutch and Rewell, 1945) that sulphonamide and penicillin can be administered and absorbed in this form and concentrations sufficient for chemotherapeutic purposes established even in the blood. Wilson and others (1945) demonstrated the curative action of such mists in experimental pneumonia, and later clinical trials both here and in America have further explored the

practical applications and limitations of the method. The phial is charged daily with 200,000 units of white crystalline penicillin dissolved in 2 ml. of sterilized water, and 2 ml. of a strong neutral solution of the selected sulphonamide are added. Soluthiazole, available as a 45 per cent. aqueous solution, is the most suitable since it dominates the same wide bacterial range as sulphathiazole, is extremely soluble in water, and forms a neutral solution. Used at half strength, as in the mixture suggested, it does not irritate the respiratory mucosa. Its combination with penicillin prevents the increase in the density of the Gram-negative flora which follows the use of penicillin alone and greatly reduces the incidence of stomatitis. Three sessions are arranged daily, one third of the solution being nebulized and inhaled on each occasion. Similar sessions are held on three consecutive days, and further series given after an interval varying with the severity of the condition from a few weeks to a few months. Timing of the various administrations can be modified indefinitely to suit the needs of any particular case.

**Specifics.**—Many of the older drugs have fallen into considerable disuse in spite of the hopeful experiences often recorded with them. Such amongst others are iodine, sulphur, thiosinamin, o-iodoxybenzoates, bee venom, and short-life radioactive derivatives of thorium and radium. It is proposed to leave their reputations in other hands and proceed to newer matters. Penicillin and sulphonamide have failed to give specific relief, although they are of great service in the treatment of septic foci, but gold still grows in popularity.

*Gold.*—About 1 mg. of gold is taken daily with the food and eliminated in the faeces (Berg, 1928). Its administration for rheumatic disease was first proposed by Feldt (1926), and clinical trials were made by Forestier (1929) and Umber (1929), with intravenous injections of gold sodium thiosulphate. During the succeeding two decades it has firmly established itself as useful therapeutically. A number of organic compounds, most of which are proprietary, have been devised. Seven or eight are mentioned in Martindale and in the U.S. Dispensatory. One of the most popular to-day is sodium aurothiomalate, which can be injected intramuscularly either as an aqueous solution or as a suspension in oil. The calcium salt is insoluble. Injected as the sodium salt, gold quickly reaches the blood, where it is carried in the plasma. The greater part of it is then deposited in the tissues and the small surplus appears in the urine. Elimination by the kidney attains a maximum on the actual day of injection. Gold finds its way into the synovial and cerebrospinal fluids, but at lower concentrations than those in the blood where a titre of 0·8 mg. per 100 ml. may be established during a standard course of therapy. Gold is released slowly from its storage depots and may continue to be excreted for many months or even a year after the conclusion of a series of injections. Insoluble compounds such as gold sulphide behave differently. They are phagocytosed and removed from the injection site so slowly that the plasma titre remains persistently low. The greater part is deposited in the liver in an inert form. The insoluble salts are less toxic than the soluble ones, but they are also less effective therapeutically.

Mode of Action.—Gold is distributed selectively in the reticulo-endothelial system including the corresponding cells at sites of chronic inflammation (Koppenhöfer, 1935) and it has been suggested that it produces its therapeutic effects by stimulating phagocytes and other defence mechanisms, but evidence is steadily accumulating in favour of the view that its action is a truly chemotherapeutic one leading more directly to the death of invading organisms. Most of the work has been done on experimental arthritis produced by streptococci and by pleuropneumonia types of organism. Schiemann and Feldt (1926) and Feldt (1926) found that gold was curative for streptococcal infections in mice. Hartung and Cotter (1941) showed in man that the bacteriostatic power of the serum for haemolytic streptococci was raised during gold treatment and that a quantitative relationship existed between the dose of gold and the degree to which the bacteriostatic power was increased. Rothbard and others (1941) found that gold would protect an infected rat from the development of joint lesions although it was not curative if given after the joints had become involved.

These results are no more than suggestive of a possible chemotherapeutic action in man, but those obtained with infections of pleuropneumonic type have been far more encouraging. Although search for the presence of such organisms in rheumatoid arthritis has so far failed, in rats they produce chronic inflammatory lesions in the joints resembling in many ways those of the rheumatoid subject. Findlay and others (1940) found that by means of gold the onset of arthritis in animals inoculated with pleuropneumonia-like organisms could be prevented. Heilman (1940) observed that sodium aurothiomalate would protect mice from otherwise lethal doses of the associated streptobacillus moniliformis, a finding confirmed by Brown and Nunemaker (1942). Sabin and Warren (1941) noted some dose-response variation for the curative action of suitable gold compounds in the chronic proliferative arthritis of rodents. With full doses given during the early stages of the disease the cure rate was almost 100 per cent. With smaller doses and when treatment was started later in the disease, the cure rate was 21 per cent. The spontaneous recovery rate in control groups was 6 per cent. Over 1,000 mice were used in these experiments, which seem to furnish

a strong case for regarding the action of gold salts in the arthritis of rodents as a chemotherapeutic one and justify a hopeful belief that gold may play an analogous part in rheumatoid arthritis as it occurs in man.

Application.—It is widely agreed that chrysotherapy is only appropriate in arthritis of chronic infective type in its active stage when the blood sedimentation rate is high. The risk of serious toxic manifestations is greatly reduced if patients with kidney, liver, skin, and cardiovascular disease are excluded and the more conservative modern scales of dosage are employed, for example intramuscular sodium aurothiomalate individual doses scaled from 0·01 g. to 0·05 g. at intervals of a week and continued to a maximum total of 0·5 g. After a rest period of two or three months to provide opportunities for elimination the injections can be continued at similar rates, but even smaller doses have been advocated by experienced workers in this field.

There are two common modes of therapeutic response: the one a long and steady improvement in the condition of the joints paralleled by a fall in the sedimentation rate and disappearance of all remnants of pyrexia, and the other a painful reaction in the affected joints and possibly a little fever following closely upon each injection. If these latter are severe they necessitate a gentler graduation of the dose and a lengthening of the inter-injection periods.

It is important that a proper background should be provided for chrysotherapy by treating infected foci and the alimentary tract thoroughly before the first injection is given. If this is done conscientiously many patients will recover without requiring gold, but in certain cases active intoxication persists until gold has been administered. When toxaemia and variations in the severity of local inflammation continue after every effort has been made to cleanse the mucosal surfaces and associated zones of focal infection, it would appear either that a specific microbic infection has been established in the joints or that the joint tissues have become so sensitized as to react violently to traces of antigen and other provocatives which would have been well tolerated by other patients. In accordance with these views it could be conceived that gold affords relief either by overcoming the microbic elements in the joint or by protecting the sensitized tissues from excessive reactions, possibly by combining with such antibodies and other receptor substances sorbed on to these tissues as are capable of reacting with blood-borne provocatives.

One of the most recent clinical summaries is that of Sundelin (1948) on 1,904 cases of rheumatoid arthritis treated with 2,817 courses of gold—principally gold thiosulphate—averaging 0·83 g. of the element per course. He reports rapid benefit in 90 per of his cases (but the later results were not assessed), a 4·5 per cent. incidence of severe complications, and a death rate of 0·36 per cent. These figures closely resemble those of Nyström (1948), who used one of the varieties of Solganal in 620 cases, giving an average of about 0·9 g. per course. The severe complication rate was 6·8 per cent. and the death rate 0·32 per cent. There were many instances of moderate leucopenia, eosinophilia, thrombocytopenia, anaemia, and albuminuria, but they were classified as minor derangements and were not allowed to interfere with the course of injections.

Antidotes.—The older treatment of toxic complications by withdrawal of the drug and the administration of thiosulphate of sodium, magnesium, or calcium has been strongly reinforced by the recent introduction of BAL, a dithiol containing protective sulphydryl groups developed as an antidote to arsenical war gases. Good results have followed its employment in dermatitis, thrombocytopenic purpura, and granulocytopenia produced by gold (Peters and others, 1947; Slot and McDonald, 1947; Cohen and others, 1947; Ragan and Boots, 1947; Simpson, 1948; Macleod, 1948). The gold attaches itself to the sulphur atoms of the BAL radicle to form a non-toxic compound. It is contra-indicated by the presence of liver damage, but kidney lesions do not preclude its use. It is supplied as a 5 per cent. solution in oil for intramuscular injection. 2 ml. are given four-hourly for four doses on the first day. Two doses are then given each day and later reduced to one, over a period of six to ten days, but larger doses have been used and the treatment kept up for several weeks.

The toxicity of gold, no less than the striking successes recorded of its use, have led to trials with other metals particularly with bismuth, copper, and aluminium, in the hope that equal benefits might be obtained at smaller risk. Aluminium administered as the acetate has so far failed to help. Bismuth and copper merit further trial.

*Bismuth.*—Bismuth compounds are comparatively non-toxic and rarely cause fatal complications. The clinical records so far published are promising but far more data are needed before the curative action of these compounds in arthritis can be admitted. They are treponemostatic *in vitro* and deprive the syphilis organism of its infective powers. By analogy it is hoped that they may act in a similarly direct manner on the presumed infective agent of rheumatoid arthritis. Many varieties are available for intramuscular injection dissolved or suspended in water and water-miscible solvents or in oil. In most compounds the bismuth plays a basic part, but in Iodobismitol (sodium iodobismuthite) and Sobisminol

(sodium bismuthate) the element is incorporated in the acid radicle. The last-mentioned substance has the distinction of being absorbed in effectively therapeutic quantities when administered by mouth (Hanzlik and others, 1937, 1938: Sollmann and others, 1938). The posology in rheumatic conditions is still in an experimental stage. The present recommendations are that individual doses should be about one-fifth of those used in syphilis with a month's interval between them at first and a gradual spacing out until three months may intervene between the eleventh dose and the final twelfth. Some of the water-soluble forms are precipitated locally after injection. They, like those which are initially insoluble, are slowly converted into tissue-soluble forms and carried away in solution. The thioglycollate is exceptional in that it is soluble not merely in water but in tissue fluids too, so that its diffusion from the injection site is accomplished very rapidly. Concentrations in the blood and the urinary excretion rate do not reach peak values until the fourth or fifth day after an injection of the salicylate but are maximal on the actual day of injection when the thioglycollate or iodobismuthite are used. As a guide to further trials it can be pointed out that oily suspensions of insoluble bismuth salicylate B.P. are absorbed slowly and exert a constant sustained action, whilst the water-soluble compounds Thiobismol (sodium bismuth thioglycollate), Iodobismitol, and Sobisminol act quickly and are suited to therapeutic pulsations of higher frequency. The normal serum-titre is about 130 $\mu$g. per 100 ml. (Brendstrup, 1948).

*Copper.*—The physiological importance of copper is well known. The element is present in food and the usual daily turnover is 2 to 2·5 mg. (Tompsett, 1934). The possible chemotherapeutic action of its organic compounds was investigated by Dixon and Hoyle (1921), but the ethylene thiocarbonate which they used did not seem to be helpful in animal tuberculosis. Fenz (1941) introduced them for the treatment of rheumatic conditions. Forestier and Certonciny (1946, 1947) and Forestier and others (1948) carried out more extensive trials using the sodium salt of cupro-allylthioureameta-benzoic acid (Cupralène, Cuprelone) intravenously and cupro-oxyquinoline-sulphonate of methylamine for intramuscular injection. Even the latter compound is irritant and is given with procaine. The diethylamine (Dicuprène) is also used. The number of cases reported is too small for statistical treatment but on the whole such clinical improvement as there may have been was not of a greater order than that following the use of gold. 5 ml. of a 10 per cent. solution of the oxyquinoline compound (=30 mg. Cu) were given two or three times a week in six-week courses with gaps of four to eight weeks. Toxic manifestations were few and not serious. Recently the old controversy as to the possible production of hepatic cirrhosis by copper has been raised again by Forbes (1947). The original suggestion came from Mallory (1926), who attributed the common type of hepatic cirrhosis known as gin-drinker's liver to copper contaminants in the spirits rather than to the alcohol. The evidence of later workers was often contradictory, and the case for the original hypothesis was never established. In view, however, of the magnitude of the doses of copper now advocated for therapeutic purposes, the possibility of its giving rise to delayed cirrhosis must be borne in mind.

**Remission Factors**

*Pregnancy.*—It is an old observation that the joint condition of women with rheumatoid arthritis often improves markedly during pregnancy and that relapse in the puerperium may be equally dramatic even before the patient has resumed her household duties. The beneficent influence may be hormonal, but eludes reproduction by hormone therapy. Possibly it depends on other chemical changes in the blood, such as the presence of the histaminolytic agent described by Anrep and others (1947) in plasma during pregnancy. They could not find it in normal blood, and the histaminolytic index "H 1" fell rapidly during the puerperium, diminishing to half values in twenty-four hours and quarter values after two days. Such a substance, possibly a histaminase enzyme, could be expected to diminish joint disturbances caused by local histamine-release during antigen-antibody interactions. The earlier work on the subject has been summarized by Ahlmark (1944). Anrep could not raise the H 1 value artificially by daily injections of histamine in either dogs or man. Transfusion with blood from pregnant women has been tried as a therapeutic measure in rheumatoid arthritis (Barsi, 1947), but the results merely reflect those of Appelqvist and Holsti (1947), who used transfusions of ordinary blood. When the case reports are compared it is impossible to discern any special advantage in using pregnancy-blood. Further research is needed before any definite therapeutic advance can be made along these lines.*

*Histamine Antagonists.*—If any considerable fraction of the joint disturbance in rheumatic diseases is caused by histamine-release, it might be expected that good use could be made of the recently introduced histamine-antagonist drugs. Mayer and Kull (1947) have produced evidence that at least one of these drugs, pyribenzamine, antagonizes hyaluronidase as well as histamine, whilst Fischel (1947) failed to find that it modified the Arthus reaction. The clinical reports of Benadryl in subacute arthritic cases in the United States Naval Reports (1948) were non-committal. My own limited experience is that Antistin sometimes gives relief from pain comparable with that of acetylsalicylic acid in osteo-arthritis and old-standing rheumatoid arthritis. Some allergic phenomena are more definitely influenced than others by these drugs. The differentiation in effect may depend

* See also article by Hench and others at p. 97 of this issue.

partly upon whether the histamine disturbance is produced intracellularly as is presumed to be the case in asthma, or extracellularly as in simple flare, but further ingenuity is needed to explain the inability of Neoantergan to antagonize the action of intravenously injected histamine on gastric secretion and the failure of pyribenzamine to control the skin response to intradermal tuberculin in tubercular subjects (Fischel, 1947).

The older Histamine-antagonists, Benadryl, Antergan, Antistin, and pyribenzamine are now supported by many others : for example, Anthallan, Decapryn, Linadryl, Anthisan or Neoantergan, Neohetramine, Chlorothen, and Bromothen, and have recently been supplemented by a new chemical series based on pyridindene, for example Thephorin, and thirdly by derivatives of phenthiazine in the form of R.P. 3277 (Phenergan), and Pyrrolate. Others will doubtless quickly follow, evoking various patterns of therapeutic response. It would not seem unreasonable, therefore, to hope that presently some useful application will be found for them in the treatment of rheumatic disorders.

*Jaundice*.—It has been noted on several occasions that in cinchophen poisoning in rheumatoid patients the onset of jaundice has been marked by a striking improvement in the condition of the joints. Hench (1938) took the matter further and recorded similar remissions during intercurrent attacks of jaundice from other causes, both obstructive and intrahepatic, although many exceptions occurred. Relapse followed quickly as the jaundice cleared. Therapeutic attempts to give relief with bile salts by mouth, human bile by stomach tube, ox bile by rectum and bilirubin and sodium dehydrocholate intravenously proved useless. Transfusions with jaundice-blood and injections of liver extract were equally disappointing. No means of copying the natural phenomenon has been found, but a promising field remains open for further research.

### Local Measures

*Intra-articular Injections*.—Disorganized joints often remain painful after toxaemia, as assessed by the sedimentation rate, has passed. This is the condition in which intra-articular injection therapy has principally been applied, although some enthusiasts also use the technique for more actively inflamed joints. Several types of solution have been used, the most popular during the past ten years being an acid solution of procaine adjusted to *p*H 5 by the addition of lactic acid, acid potassium phosphate, or ascorbic acid (Waugh, 1938 and 1946; Crowe, 1944; Leon, 1948). The object is to provoke a mild inflammatory response with a local leucocytosis in the anticipation that in the aftermath of repair the joint will become more comfortable. Baker and Chayen (1948) confirmed the findings but obtained equally satisfactory results with neutral solutions of procaine in isotonic saline using 10 ml. for a hip or knee, 5 ml. for the shoulder, and 1 ml. for the thumb. They attributed the benefits to the psychological effect of the prompt relief afforded by the procaine and to the lubricant action of the injected fluid. Even alkaline solutions appear to be helpful. Kron (1948) used isotonic sodium bicarbonate (1·29 per cent.) and injected 0·5 ml. to 2 ml. on alternate days for two to four doses.

*Liniments*.—Experiments in which referred pains have been evoked by the injection of fluid into the interspinous ligaments have shown that the pain can be abolished by the injection of a local anaesthetic into the skin of the area to which the pain is referred. Conversely, positive stimulation of a pleasant kind applied to the same cutaneous areas also reduces the pain; for example, the tingling of aconite, the coolness of menthol, and the warmth of the rubefacients. These means can be variously combined to suit the individual needs of the patients. When there is much skin hyperaesthesia, as in neuritis, the local analgesics must be stressed and the positive stimulants applied with caution. Perhaps the most useful for this purpose are benzyl alcohol and salicyl alcohol (saligenin) as 5 to 10 per cent. solution in a skin-penetrating lipoid solvent such as terpineol. All three substances are mildly stimulant also but their combined effect is reduction of hyperaesthesia. The unwanted stimulant element can be reduced without interfering with the analgesic action by replacing some of the terpineol with alcohol up to 20 per cent. It can be increased by adding mildly stimulant rubefacients such as methyl salicylate and camphor. In the absence of cutaneous tenderness, stimulation can be applied more robustly by means of the stronger official liniments of the Pharmacopoeia, care being taken not to blister the skin or produce a rash. The superficial hyperaemia thus established is accompanied by deep reflex vasodilatation, which it is hoped may exert a healing influence on the damaged joints. The mechanism resembles that of radiant heat therapy, in which deep hyperaemia is produced reflexly in response to the heating of the surface layers of the skin. Many substances when dissolved in lipoid solvents of low surface tension penetrate the skin and reach the blood stream. Amongst those of importance in rheumatic diseases are the esters of salicylic acid, acetyl-salicylic acid, and phenyl-cinchoninic acid, which are all absorbed freely by this route. The amyl ester is generally used in the case of phenyl-cinchoninic acid, and the methyl esters of the other two compounds. They produce a small but useful degree of skin

stimulation but after absorption do not reach the sites of their various antirheumatic activities any more quickly than they would have done had they been absorbed from the alimentary canal. They do, however, escape the chemical interference and censorship of the liver and the gut.

**Muscular Relaxation.**—For nocturnal cramps the muscle depressant action of quinine is often useful, but the ideal drug for securing continuous relaxation of muscle spasm in active arthritis has still to be found. Several are on trial. The one in longest use is neostigmin (Prostigmin) although its *modus operandi* in this connexion is difficult to discern. Its chief action is to inhibit cholinesterase and so increase the effectiveness of acetylcholine released at the myoneural junction on stimulation of the motor nerve. This is believed to be the basis of its utility in myasthenia gravis, and it might be expected to lead to an increase rather than a decrease in the tonus of spastic muscles. It can be given in 15 mg. tablets by mouth once or twice a day or 1 mg. subcutaneously daily, combined with an adjusted dose of atropine or belladonna to antagonize some of its unwanted effects. Injection is often followed by a short period of diminished pain, but sometimes it appears to aggravate the discomfort. Trommer and Cohen (1944) spoke well of it but later clinical reports have not justified the enthusiasm of earlier users (Lucchesi and Lucchesi, 1945-6, 1946).

More recently introduced drugs, clinically in an experimental stage, are Parpanit, a compound related chemically to pethidine, and Trasentin, an atropine-like drug, used with success in Parkinsonism and experimentally causing marked diminution in muscle tone (Heymans and de Vleeschouwer, 1948). Myanesin, an α-glycerol ether devised as a substitute for curare, produces complete muscle relaxation, and if the dose is correctly adjusted there is no interference with respiration (Berger and Bradley, 1946, 1947). Its properties differ in many ways from those of curare, but both drugs exert a strongly depressant action on striated muscle at the myoneural junction. It is absorbed satisfactorily from the stomach and after absorption is quickly metabolized so that its effect is not of any long duration. The transience of its action may restrict its use in protracted medical conditions and its application to the problems of arthritis awaits elaboration.

**Analgesics.**—The specific relief afforded by salicylates, colchicum, and cinchophen has already been discussed. There are other drugs with wider fields of effectiveness and special indications. Acetyl-salicylic acid in its many guises is familiar to all. Of the pyrazolon derivatives, amidopyrine has already been mentioned. The other member of the group, phenazone or antipyrine, is not quite so effective but is free from the stigma of causing agranulocytosis. It has been in service since 1884. Acetanilide from aniline and phenacetin (aceto-phenetidin) from p-aminophenol are almost as ancient and are approximately equivalent in power. They too have never been known to depress the white cell count dangerously. But these three safe analgesics lack the specificity of amidopyrine in acute rheumatic fever. The general public consumes them in considerable amounts. Cases of chronic poisoning are therefore not rare although difficult to diagnose since the symptoms resemble those of other common conditions. They include anorexia, loss of weight, anaemia, weakness, short windedness, indigestion, and insomnia, whilst the blood changes on which the common tinge of cyanosis depends may be difficult to analyse in the laboratory. Kryofine (methoxy-aceto-phenetidin), Phenamide (phenocoll hydrochloride), and lactyl-p-phenetidin belong to the phenacetin group whilst Exalgin is an acetanilide derivative. The phenyl semicarbazides form a fourth chemical group, represented by Cryogenine, now defined as 1-phenylsemicarbazide (FrCx) and formerly as 3-semicarbazidobenzamide (Lumière), safe analgesics with therapeutic activity approximating to that of phenacetin. Often, as in the treatment of sciatica, more powerful analgesics are required. Morphia has frequently been used, but tolerance is soon acquired and it is not only causes addiction but may lead to gross alimentary derangement. It is very difficult to cure any form of rheumatism in a persistently constipated patient. Its isomer dihydromorphinone, better known as Dilaudid, does not cause constipation. It is about ten times as powerful as morphine. A useful dose for oral administration is 2·5 mg., and the maximum 4 mg., which can be repeated with safety up to three times in twenty-four hours. Its narcotic effect is variable but not great. Metopon, another morphine derivative, has recently appeared in America and the reports of its properties suggest that in respect of pain relief, narcosis, and constipating action it occupies an intermediate position between morphine and Dilaudid.

Pethidine (Dolantin, Dolantal, Demerol) belongs to an entirely different chemical class and structurally is related to atropine. It was synthesized by Eisleb and Schaumann (1939), but only became available in England during the later stages of the world war 1939-45. It can be used by mouth for the relief of pain and in 25 mg. doses produces definite euphoria but it does not cause narcosis unless larger doses are given. It does not cause constipation, and its additional action of allaying hypertonus in plain muscle may even correct constipation of the spastic type. Work done on various

German formulae has given us amidone, known variously as Physeptone, Miadone, and Methadon. Dolophine is probably identical, although the structural formula given does not always agree exactly with that attributed to amidone. The average analgesic dose for oral use is 10 mg., but 5 mg. are often sufficient. Scott and his co-workers (1947) reported its use in joint conditions and found that although it usually controlled osseous pains it was not so consistently effective against pains of articular origin. For the pain arising from ischaemic muscle, Hewer and Keele (1947) found it to be as effective as morphine and far more effective than pethidine. It may cause a little nausea and constipation, but not of the same degree as that following the use of morphine. Euphoria is rarely noticed. Nevertheless, both amidone and pethidine have been placed under the control of the D.D.A. regulations after very careful official consideration of their qualities. The most recent of the heptanone series to be tried clinically is " C.B.11 " (Heptalgin). Wilson and Hunter (1948) demonstrated that it could be used to relieve the pain of ischaemic muscle, but did not find it as useful as amidone for this purpose. They also reported some analgesic action in sciatica, but their cases were not sufficiently numerous for analysis.

**Various General Measures.**—In attempts to override the evasive aetiological factors at work in rheumatism, drugs are sometimes used which in their effects of producing fever and leucocytosis simulate the natural defence mechanism of the body. On other occasions substantial doses of endocrines, vitamins, and other physiological substances have been given. Leucocytosis can be sustained by drugs for short periods only. That following the injection of sodium nucleinate or pentnucleotide fades away after a week of daily medication. Sulphur by vein causes a substantial increase in the polymorphonuclear count, but its duration is only a matter of hours and injections cannot be repeated many times. Pyrexia accompanies the sulphur leucocytosis and it has sometimes been thought that the combined effects of fever and leucocytosis have been helpful. Colloidal sulphur injected intramuscularly produces a similar dual response of less intensity, but may lead to considerable damage to the muscle. It is now agreed that the pharmacological reactions are inconstant and the clinical effects uncertain so that in spite of the early enthusiasm of Cawadias the Council on Pharmacy of the American Medical Association reported that by 1933 the practice of injecting sulphur into either the muscles or the veins had almost been abandoned in America.

*Endocrines.*—A rheumatic patient with well-defined endocrine defects is greatly benefited by their correction. Some years ago it was the vogue to prescribe small doses of thyroid preparations in the chronic and subacute phases of rheumatoid arthritis irrespective of whether there were clinical signs of deficiency or not. This led to little good and cannot be recommended, but spectacular success often follows thyroid medication in myxoedematous rheumatic subjects. Sex hormones have also been tried extensively, especially oestrogenic ones in women for arthritis arising during the menopausal decade. It had been expected that they might be of particular value in that somewhat ill-defined clinical group styled climacteric arthritis, which affects principally the knees and the small joints of the fingers, but no consistent results have been obtained. Coste and others (1948) used hexoestrol, 5 mg., and alternatively stilboestrol, 3 mg. to 4 mg., daily for ten consecutive days each month and noted a transient diminution in symptoms in a little more than half of his 205 osteo-arthritic patients. Pierre-Weil and Sichère (1948) used implants of oestradiol and progesterone and record a reduction in pain in 50 per cent. of menopausal and post-menopausal women with osteo-arthritis. It would appear that some advantage can on occasion be secured by the method in these intractable cases, but if oestrogens are administered too generously the endometrium becomes hyperplastic and troublesome uterine haemorrhage occurs. Administration must be carefully supervised. The following dosage schemes are appropriate but no final recommendations can be made: (1) injections of natural oestrogen, 50,000 international benzoate units twice a week for several weeks after which the dose should be systematically reduced; (2) synthetic dinoestrol by mouth, 0·3 mg., or ethinyl oestradiol, 0·05 mg. daily for nine or ten consecutive days in each month over a span of three or four months in all. (See also p. 97 of this issue.)

*Vitamins.*—Variations in the prothrombin-content of the blood are of frequent occurrence during rheumatic fever. Their relationship to salicylate medication is not simple. Significant falls may take place before salicylate therapy has been instituted or may be found during the administration of the drug and may correct themselves spontaneously even though the course of mild or massive salicylate dosage is not interrupted (Owen and Bradford 1946). There would appear to be little justification for giving vitamin K or its analogues as a routine adjunct to salicylates. Vitamin K could logically be reserved for definite hypothrombinaemia complicated by haemorrhage and for those rare occasions

when surgical operation is contemplated for a rheumatic patient in a hypothrombinaemic phase.

The dietetic restrictions commonly imposed on rheumatic patients expose them to the risk of primary vitamin deficiencies which can easily be made good with supplementary vitamin concentrates. Vitamin D has been employed for different reasons in massive dosage in the treatment of a variety of conditions, including several forms of arthritis. By an inductive method of reasoning it was surmised that it might normalize bony growth and metabolism in the affected parts, re-calcify the rarefied areas, and generally increase resistance to microbe invasion, but the clinical results do not bear out such hopeful anticipation. Calciferol, 50,000 i.u. daily for a week and then at two-day intervals, has been used without much evidence of harm, but in the treatment of arthritis daily doses up to 600,000 i.u. have been advised and these may cause renal failure and serious and even fatal metastatic deposits of calcium in the soft tissues. Ostelin (high-potency) was given by Lightbound (1948) in 150,000 i.u. daily by mouth or 600,000 i.u. intramuscularly twice a week for six months without disaster. The kidney function was impaired in all cases, and hypercalcaemia associated with symptoms of toxic action commonly occurred. The ostelin appeared to be better tolerated when injected than when given orally. The tendency of irradiated ergosterol to produce such lesions is greatly influenced by the circumstances in which irradiation has been carried out, and it was hoped that the special method employed in producing the American variety Ertron would overcome the difficulties. Giving Ertron in 150,000 U.S.P. units (U.S.P. units are equivalent to international units) daily and increasing the dose very gradually to 300,000 units, Norris (1947) reported improvement in pain and swelling in about half of his forty miscellaneous cases of predominantly rheumatoid types. Gastric disturbances occurred frequently, but no other adverse reactions were noted. Nevertheless, fatalities from massive metastatic deposits of calcium salts have occurred amongst arthritic patients receiving this preparation (Kaufman and others, 1947; Bevans and Taylor, 1947), and the procedure should definitely be regarded as a dangerous one and its advantages in rheumatism problematical.

## Summary

The medicinal measures of most proven worth in the treatment of rheumatoid arthritis and other rheumatic conditions of chronic inflammatory type are those concerned with (1) cleansing areas of surface infection, (2) correcting alimentary aberrations, (3) maintaining the efficiency of vital functions, (4) relieving pain and distress, and (5) chrysotherapy.

Other methods have been examined; some have been discarded and others hopefully recommended for further research and trial.

(The above summary refers to the section of this article dealing with the rheumatoid group, and not to the paper as a whole, which does not seem to lend itself to helpful condensation.)

## References

Ahlmark, A. (1944). *Acta physiol. scand.*, **9**, Supplement 28.
Anrep, G. V., Barsoum, G. S., and Ibrahim, A. (1947). *J. Physiol.*, **106**, 379.
Appelqvist, O., and Holsti, O. (1947). *Schweiz. med. Wschr.*, **77**, 977.
Baker, D. M., and Chayen, M. S. (1948). *Lancet*, **1**, 93.
Barsi, I. (1947). *Brit. med. J.*, **2**, 252.
Bélisle, M. (1948). *Un. méd. Can.*, 77, 392.
Berg, R. (1928). *Biochem. Z.*, **198**, 424.
Berger, F. M., and Bradley, W. (1946). *Brit. J. Pharmacol.*, **1**, 265.
——, —— (1947). *Lancet*, **1**, 97.
Berger, F. M., and Schwartz, R. P. (1948). *J. Amer. med. Ass.*, **137**, 772.
Bevans, M., and Taylor, H. K. (1947). *Amer. J. Path.*, **23**, 367.
Brendstrup, P. (1948). *Ugeskr. Læg.*, **110**, 948.
Bloch, L., and Rosenberg, D. H. (1934). *Amer. J. Digest. Dis.*, **1**, 29.
Bowen, B. D., Roufa, J. F., and Clinger, O. W. (1936). *J. Amer. med. Ass.*, **107**, 276.
Brown, T. McP. and Nunemaker, J. C. (1942). *Bull. Johns Hopk. Hosp.*, **70**, 201.
Coburn, A. F. (1943). *Ibid.*, **73**, 435.
——, and Moore, L. V. (1939). *J. clin. Invest.*, **18**, 147.
Cohen, A., Goldman, J., and Dubbs, A. W. (1947). *J. Amer. med. Ass.*, **133**, 749.
Coste, F., Lacronique, A., and Hochfeld, M. (1948). *Rev. Rhum.*, **15**, 40.
Crowe, H. W. (1944). *Lancet*, **1**, 563.
Dameshek, W., and Colmes, A. (1936). *J. clin. Invest.*, **15**, 85.
Dixon, W. E., and Hoyle, C. (1921). *J. pharm. exp. Therap.*, **35**, 409.
Dry, T. J., Butt, H. R., and Scheifley, C. H. (1946). *Proc. Mayo Clin.*, **21**, 497.
Eisleb, O., and Schaumann, O. (1939). *Dtsch. med. Wschr.*, **65**, 967.
Feldt, A. (1926). *Klin. Wschr.*, **5**, 299.
Fenz, E. (1941). *Munch. med. Wschr.*, **88**, 1101.
Findlay, G. M., Mackenzie, R. D., and McCallum, F. O. (1940). *Brit. J. exp. Path.*, **21**, 13.
Fischel, E. E. (1947). *Proc. Soc. exp. Biol. N.Y.*, **66**, 537.
Forbes, G. (1947). *Brit. med. J.*, **1**, 367.
Forestier, J. (1929). *Bull. mém. Soc. méd. Hôp. Paris*, **53**, 323.
——, and Certonciny, A. (1946). *Presse med.*, **54**, 884.
——, —— (1947). *Rev. Rhum.*, **14**, 271.
——, Jacqueline, F., and Lenoir, S. (1948). *Presse méd.*, **56**, 351.
Gebert, K. (1931). *Z. klin. Med.*, **117**, 147.
Gersdorff, W. A., and Smith, L. E. (1940). *Amer. J. Pharm.*, 197.

Griffith, G. C. (1947). *J. Amer. med. Ass.*, **133**, 974.
Guerra, F., and Gil, J. R. (1946). *Arch. Inst. Cardiol. Mex.*, **16**, 293.
—, — (1947). *Ibid.*, **17**, 733.
Hanzlik, P. J., Lehman, A. J., and Richardson, A. P. (1937). *Amer. J. Syph.*, **21**, 1.
—, —, — (1938). *J. Pharmacol. exp. Therap.*, **62**, 54.
Harris, T. N. (1947). *Amer. J. med. Sci.*, **213**, 482.
Hartung, E. F., and Cotter, J. (1941). *J. Lab. clin. Med.*, **26**, 1274.
Heilman, F. R. (1940). *Science*, **91**, 366.
Hench, P. S. (1938). *Arch. int. Med.*, **61**, 451, 495.
Hewer, A. J. H., and Keele, C. A. (1947). *Lancet*, **2**, 281.
Heymans, C., and de Vleeschhouwer, G. R. (1948). *Arch. int. Pharmacodyn.*, **75**, 307.
Kaufman, P., Beck, R. D., and Wiseman, R. D. (1947). *J. Amer. med. Ass.*, **134**, 688.
Klarmann, E., Shternov, V. A., and Gates, L. W. (1934). *J. Lab. clin. Med.*, **19**, 835 ; **20**, 40.
Koppenhöfer, G. F. (1935). *Beitr. klin. Tuberk.*, **86**, 549.
Kron, R. (1948). *Schweiz. med. Wschr.*, **78**, 80.
Leon, M. de (1948). *Ned. Tijdschr. Geneesk.*, **92**, 2084.
Lightbound, Teresa (1948). *Lancet*, **2**, 1010.
Lucchesi, M., and Lucchesi, O. (1946). *Hospital, Rio J.*, **30**, 951.
—, — (1945-6). *Annals of the Rheumatic Diseases*, **5**, 214.
MacBryde, C. M. (1940). *J. Amer. med. Ass.*, **114**, 316.
Machle, W., Deichmann, W., and Thomas, G. (1943). *J. industr. Hyg.*, **25**, 192.
Macleod, J. G. (1948). *Annals of the Rheumatic Diseases*, **9**, 143.
Mallory, F. B. (1926). *Arch. int. Med.*, **37**, 336.
Manchester, R. C. (1946). *Ibid.*, **78**, 170.
Mayer, R. L., and Kull, F. C. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 392.
Meleney, F. L., Johnson, B. A., and Pulaski, E. J. (1946). *J. Amer. med. Ass.*, **130**, 121.
Meyer, K., and Ragan, C. (1948). *Science*, **108**, 281.
Mutch, N. (1934). *J. Pharmacol.*, **51**, 112.
— (1944). *Lancet*, **2**, 775.
— (1946). *Quart. J. Pharm. Pharmacol.*, **19**, 490.
Mutch, N., and Rewell, R. E. (1945). *Lancet*, **1**, 650.
Norris, G. (1947). *Rheumatism*, **3**, 106.
Nyström, G. (1948). *Nord. Med.*, **37**, 499.
Owen, G. C., and Bradford, H. A. (1946). *Ann. int. Med.*, **25**, 97.
Peters, R. A., and others (1947). *Brit. med. J.*, **2**, 520.
Pierre-Weil, M., and Sichère, R. (1948). *Rev. Rhum.*, **15**, 33.
Ragan, C., and Boots, R. H. (1947). *J. Amer. med. Ass.*, **133**, 752.
Reid, J. (1948). *Quart. J. Med.*, **17**, 139.
Renshaw, A. (1947). *Annals of the Rheumatic Diseases*, **6**, 15.
Rosenblum, H., and Fraser, L. E. (1947). *Proc. Soc. exp. Biol. N.Y.*, **65**, 178.
Rothbard, S., Angevine, D. M., and Cecil, R. L. (1941). *J. Pharmacol.*, **72**, 164.
Sabin, A. B., and Warren, J. (1941). *J. Amer. med. Ass.*, **117**, 1561.
Schiemann, O., and Feldt, A., (1926). *Z. Hyg. Infekt. Kr.*, **106**, 83.
Schiffrin, M. J., and Komarov, S. A. (1941). *Amer. J. Digest. Dis.*, **8**, 215.
Scott, C. C., Kohlstaedt, K. G., and Chen, K. K. (1947). *Curr. Res. Anaesth.*, **26**, 12.
Simpson, N. R. W. (1948). *Brit. med. J.*, **1**, 545.
Slot, G., and McDonald, A. D. (1947). *Ibid.*, **2**, 773.
Snyder, R. G., and others (1935). *Proc. Amer. Ass. Study and Control of Rheum. Dis.*, **2**, 101.
Sollmann, T., Cole, H., and Henderson, K. (1938). *Arch. Derm. Syph. Chicago*, **37**, 993.
Stokes, H. L. (1947). *Proc. R. Aust. Coll. Phys.*, **2**, 16.
Sundelin, F. (1948). *Nord. Med.*, **37**, 303.
Svartz, N. (1948). *Ibid.*, **37**, 299.
— (1948). *Bull. Schweiz. Aked. med. Wiss.*, **3**, 311.
Swyer, G. I. M. (1948). *Biochem. J.*, **42**, 28.
Thomas, C. B., and France, R. (1939). *Bull. Johns Hopk. Hosp.*, **64**, 67.
Tompsett, S. L. (1934). *Biochem. J.*, **28**, 1544, 2088.
Trommer, P. R., and Cohen, A. (1944). *J. Amer. med. Ass.*, **124**, 1237.
Umber, F. (1929). *Med. Welt.*, **3**, 593, 633.
U.S. Naval Medical Research Unit (1948). *U.S. Nav. med. Bull. Wash.*, **48**, 380.
Warren, H. A., Higley, C. S., and Coombs, F. S. (1946). *Amer. Heart J.*, **32**, 311.
Waugh, W. G. (1938). *Lancet*, **1**, 487.
— (1946). *Brit. med. J.*, **2**, 876.
White, E. P. C. (1931). *J. Lab. clin. med.*, **17**, 17.
Wilson, W. M., and Hunter, R. B. (1948). *Brit. med. J.*, **2**, 553.
Wilson, C. E., Hammond, C. W., Byrne, A. F., and Bliss, E. A. (1945). *Bull. Johns Hopk. Hosp.*, **77**, 411.

## Traitement Médical de Troubles Rhumatismaux

RÉSUMÉ

Les médicaments qui se sont montrés les plus actifs dans le traitement de l'arthrite rhumatismale et d'autres affections rhumatismales du type inflammatoire chronique sont celles dont le rôle consiste (1) à nettoyer les foyers d'infection superficiels, (2) à corriger les fautes alimentaires, (3) à maintenir la bonne marche des fonctions vitales, (4) à soulager la douleur et relever le moral du malade, (5) et la chrysothérapie.

D'autres méthodes ont été étudiées; certaines ont été rejetées, et d'autres sont recommandées pour une étude plus approfondie.

(Le résumé ci-dessus se rapporte à la partie de cet article qui a trait au groupe des affections rhumatismales, et non à l'ensemble de l'article, qui ne se résumé pas aisément.)

# MASSIVE SALICYLATE THERAPY IN RHEUMATIC FEVER

BY

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Salicylates were first advocated for the treatment of rheumatic fever by Stricker in 1896. Lees in 1903 suggested that salicylates, if used in large dosage, had a true anti-rheumatic effect, but the majority of clinicians considered that the improvement brought about by salicylate therapy was confined to the relief of symptoms. Interest in this work was reawakened in 1943 when Coburn claimed that intensive salicylate therapy reduced the period of active infection and the incidence of permanent valvular damage, and that it controlled relapses. Coburn's work stimulated reinvestigation of the problem; excellent reviews have recently been published by Manchester (1946) and Taran and Jacobs (1945), and by Parker (1948) in this country. Not all investigators confirm Coburn's work, and it has been criticized by Warren and others (1946) and by Harris (1947).

## Clinical Data and Methods Used

The present study describes results of salicylate therapy on eighty recruits at three R.A.F. reception and training centres who developed rheumatic fever between April 1947, and July 1948. All were aged 18 except two, whose ages were 23 and 26. All but three were men, and fifteen (18·8 per cent.) admitted to a history of previous rheumatic fever. A history of recent upper-respiratory-tract infection was obtained in 71·2 per cent., haemolytic streptococci being cultured from a throat swab on admission in twenty-nine of fifty-five cultured (53 per cent.). An average period of 2·1 weeks occurred between the precipitating infection and the rheumatic attack.

The diagnosis was established on criteria described by Jones in 1944. Patients were strictly confined to bed and temperatures were recorded four-hourly in the acute stage. Routine cardiac examination was performed frequently, and the patients were questioned daily concerning their arthralgia. The blood sedimentation rate (B.S.R.) was estimated weekly using Westergren's method without correction for the packed cell volume, as in no case did significant anaemia develop. Plasma salicylate levels were determined by the method of Brodie and others (1944). Patients received oral salicylates until a weekly B.S.R. had been normal on three consecutive occasions. No treatment was given for a further week, and rest in bed was still enforced. If the B.S.R. remained normal gradual mobilization extending over three months was undertaken, when, if the patient was progressing favourably, a month's sick leave was granted. On re-admission a careful clinical and radiological cardiac assessment was made before discharge. Cases were classified as showing either (*a*) permanent valvular damage, or (*b*) potential heart disease (cases in which systolic murmurs had persisted unassociated with radiological or clinical cardiac enlargement). Cases were observed for periods of from six to fifteen months.

## Dose of Salicylates

Three groups of patients were studied at three station hospitals employing varying salicylate dosage. Groups were comparable in numbers, in severity, and in the incidence of previous rheumatic attacks.

**Group 1.**—This group consisted of twenty-five cases; in fourteen salicylates were withheld, but the rest received small doses not exceeding 100 gr. daily.

**Group 2.**—This group comprised twenty-nine cases receiving 200 gr. of salicylates daily without blood-level control; ten received in addition 100 gr. of sodium bicarbonate daily.

**Group 3.**—Group 3 contained twenty-one cases in whom adequate salicylate levels exceeding 30 mg. per cent. were maintained by massive oral therapy. Dosage in this group showed large individual variation, from 120 to 600 gr. daily, thus anticipating the complexities of salicylate dosage recently ably described by Maggioni (1948) and by Parker (1948).

We were able to confirm Parker's observations that effective salicylate therapy could only be obtained by four-hourly oral administration of freshly made salicylate solutions in doses of 18 gr. per stone of body weight. Alkalis accelerated the urinary elimination of salicylates and required an increase of 2 gr. per stone in the dose of salicylates employed. Dehydration caused a rapid increase in the serum concentration, and was prevented by ensuring that fluid intake exceeded three pints daily. Variation in the daily excretion due to an alteration of the urinary *p*H, a deterioration in mixtures and in the crystalline salicylate used in dispensing the mixtures, and a tolerance developing after prolonged administration, caused further difficulties. These factors necessitated frequent blood-level determinations as long as therapy was maintained.

### Results of Treatment

**Effect of Temperature.**—In the twenty-five cases receiving minimal doses of salicylates it was found that fever persisted for an average of 22·7 days (highest 42, lowest 3). Those on moderate dosage became afebrile in an average of 5·1 days (highest 20, lowest 1), while those on massive dosage were rendered afebrile in an average of 1·9 days (highest 4, lowest 1). In massive therapy the febrile period was therefore significantly reduced and the strain on the heart was lessened.

**Effect on Arthalgia.**—Cases receiving little or no salicylates did not become free from pain for an average time of 22·7 days (highest 60, lowest 4); those on moderate dosage in 6·1 days (highest 50, lowest 1); the twenty-one cases receiving massive salicylate therapy became free from pain in an average of 1·9 days (highest 4, lowest 1). A significant reduction in the period of discomfort to the patient could therefore be obtained by massive treatment.

**Effect on the B.S.R.**—As the B.S.R. is the best single pathological test for the assessment of activity of the rheumatic state, its rate of return to normal in salicylate therapy is of particular interest.

In the twenty-five patients receiving minimal salicylate dosage the average B.S.R. on admission was 69·1 mm. per hour (highest 120, lowest 15), and it returned to normal in an average of 73·6 days (highest 250, lowest 10).

In the twenty-nine patients receiving moderate salicylate dosage the disease process appeared to be of comparable severity, for the average B.S.R. on admission was 45·7 (highest 116, lowest 12) and it returned to normal in an average of 37·0 days (highest 80, lowest 14).

The twenty-one patients on massive therapy appeared to contain more severe cases, as the average B.S.R. on admission was 73·1 mm. per hour (highest 122, lowest 25). Despite this the B.S.R. became normal in a significantly reduced period of 16·6 days (highest 30, lowest 7).

The difference between the groups can also be demonstrated if the number of patients showing a raised B.S.R. at weekly intervals is studied (Fig. 1). In Group 1 fourteen of the twenty-five patients studied showed a raised B.S.R. after six weeks, fourteen after eight weeks, and nine after twelve weeks; and even after twenty weeks one B.S.R. still remained elevated. In the second group all but nine of twenty-nine cases studied had returned to normal in four weeks, and all but five in six weeks, and all were normal in twelve weeks. In the group receiving massive therapy all cases showed a normal B.S.R. in five weeks.

It is interesting here to describe two cases receiving moderate dosage in which B.S.R. was rapidly controlled once an adequate level was obtained (Fig. 2).

*Case 1.*—A 23-year-old aircraftsman was admitted with acute rheumatic fever with carditis, his B.S.R. on admission being 75 mm. per hour. He was given 200 gr. of salicylate and became rapidly free from pain and afebrile. His B.S.R. fell slowly, but after six weeks had reached 15 mm. per hour. In the next four weeks the B.S.R. steadily mounted and after ten weeks had reached 40 mm. per hour. A salicylate level done at this time was found to be only 8 mg. per 100 c.cm. of blood. With an increase of dosage to 300 gr. a therapeutic level of 40 mg. was rapidly established. Within a week the B.S.R. had fallen to normal, and the patient made an uninterrupted recovery.

*Case 2.*—An 18-year-old recruit developed acute rheumatic fever with carditis and was admitted with a B.S.R. of 108 mm. per hour. He was given 200 gr. of sodium salicylate and became rapidly afebrile and free from pain. There was a slow undulant fall in his B.S.R., and after six weeks it remained at 75 mm. per hour. An estimation of the salicylate content of the plasma at this time showed it to contain 8 mg. per 100 c.cm. The dose was increased to 300 gr. daily and a therapeutic level of 42 mg. was quickly reached. There was a rapid fall in the B.S.R. which reached 28 mm. per hour in one week and became normal in three.

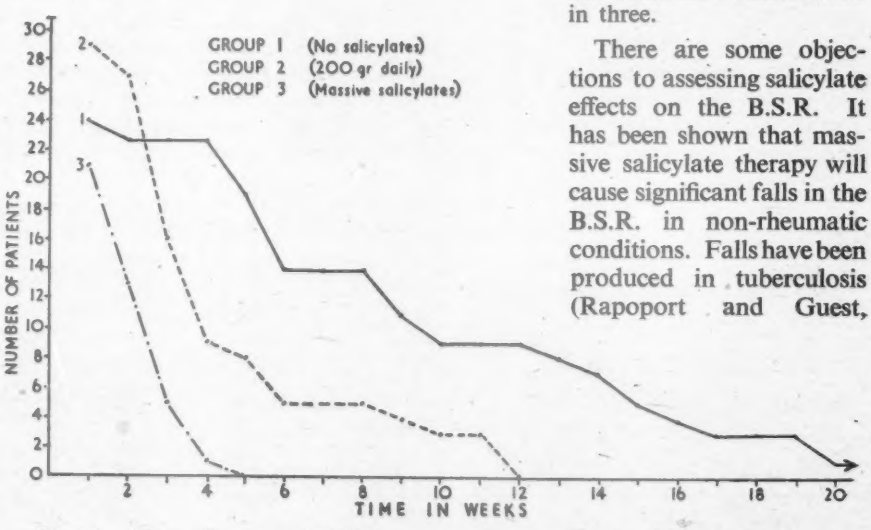


FIG. 1.—Rate of return of B.S.R. to normal on varying salicylate dosage.

There are some objections to assessing salicylate effects on the B.S.R. It has been shown that massive salicylate therapy will cause significant falls in the B.S.R. in non-rheumatic conditions. Falls have been produced in tuberculosis (Rapoport and Guest,

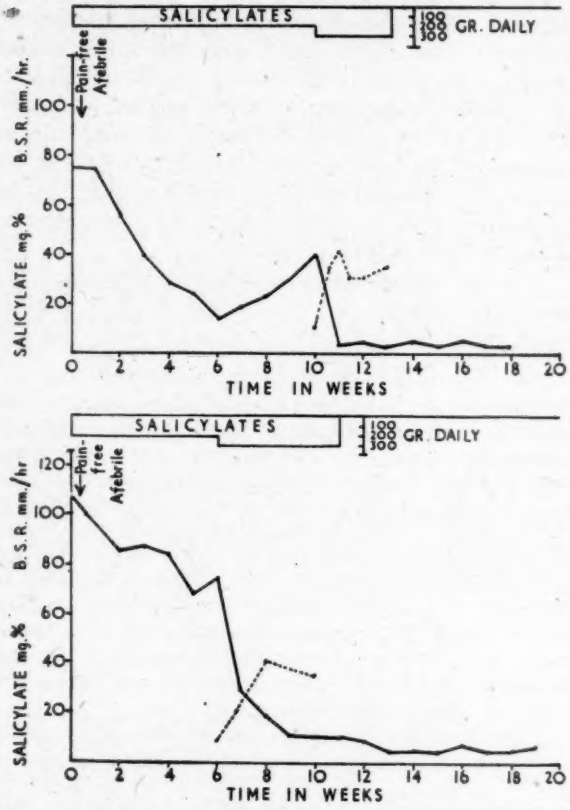


FIG. 2.—Rapid fall in B.S.R. on establishing adequate salicylate level.

1946), in carcinomatosis (Homburger, 1946) and in tuberculosis and rheumatoid arthritis (Harris, 1947). The number of cases studied, however, was small, the falls in B.S.R. produced were not of the order seen in rheumatic fever, and the B.S.R. tended to rise sharply when therapy was suspended. Five cases suffering from tuberculous pleural effusions were given large doses of salicylates. In four a significant reduction of the B.S.R. occurred, up to 40 per cent. of the initial figure, but all the B.S.R.s rose sharply when therapy was discontinued. An investigation is proceeding on larger numbers of non-rheumatic cases to see if the reduction of the B.S.R. produced by salicylate therapy is a non-specific effect due to alterations of the plasma proteins or a true anti-rheumatic effect.

**Effect on Relapses.**—Both Coburn (1943) and Manchester (1946) claimed that polycyclic relapses were significantly reduced in cases receiving massive salicylate therapy. In the present series six relapses occurred in the control group, one in the moderate-dose group, and four in the massive-dose group. Although the number of cases here is too small to draw definite conclusions it would not appear that a significant reduction of relapses had been produced by massive salicylate therapy.

The effects of the drug on fever, arthralgia, B.S.R., and relapses are summarized in Table 1.

**Effect on Carditis.**—The present survey was not of sufficient length to assess whether the incidence of permanent cardiac damage had been reduced. It is interesting to compare the figures obtained by previous authors; these are summarized in Table 2. In the short time surveys so far reported there would seem to be much difference in the results obtained, and the figures quoted by Coburn must be considered on the optimistic side. A long-term survey with controls over a period of years would be required to make sure if permanent cardiac damage can be reduced by massive therapy.

**Effect on Pericarditis.**—It is in acute rheumatic pericarditis that salicylate therapy exerts a dramatic effect. Warren and others (1945), in an otherwise unenthusiastic paper on salicylate therapy, agree that in acute pericarditis salicylates appear to exert an anti-rheumatic effect. Four cases of pericarditis were seen in this series and responded well. One case in whom a steady therapeutic level was found difficult to maintain is of particular interest here as it shows the beneficial effect of salicylate on both pericarditis and B.S.R.

TABLE 1
VARIOUS EFFECTS OF SALICYLATE THERAPY

| Group | No. of cases | Previous rheumatic fever | Dosage of salicylate (in gr. daily) | Days before afebrile | Days before free from pain | Average B.S.R. on admission. In mm./hr. | Days before normal | Relapses |
|---|---|---|---|---|---|---|---|---|
| Group 1 | 25 | 4 | 14 Nil; 11 less than 100 | 19·6 | 22·6 | 69·1 | 73·6 | 6 |
| Group 2 | 29 | 6 | 200 | 5·1 | 6·1 | 45·7 | 37·0 | 1 |
| Group 3 | 21 | 5 | 120-600 | 1·9 | 1·9 | 73·1 | 16·6 | 4 |

*Case 3.*— An 18-year-old recruit was admitted with acute rheumatic fever, his B.S.R. on admission was 96 mm. per hour. He received 200 gr. of salicylates and became rapidly free from pain. The blood level after two days was 37 mg. One week after admission the B.S.R. had fallen to 70 mm., but at this time he developed precordial pain and pericardial friction. A week later his B.S.R. had fallen to 40 mm., friction was still present, and it was found that the blood salicylate level was now only 18 mg. At the beginning of the third week the B.S.R. remained unchanged, friction persisted, and the salicylate level was now only 12 mg. per 100 c.cm. of blood. Salicylate dosage was accordingly increased to 300 gr. and was maintained at this level for the next two weeks. This caused a dramatic fall in the B.S.R. to 8 mm. per hour, and friction disappeared a few days later. Salicylate levels on this dosage were found to be 40 and 35 mg. per 100 c.cm. After five weeks, in view of the improvement of the patient, dosage was reduced to 200 gr. Two days later friction recurred, and it was found that the B.S.R. had risen sharply to 40 mm. per hour and that the blood salicylate level had fallen to 15 mg. per 100 c.cm. The establishment of a therapeutic blood level of 35 mg. per 100 c.cm. again caused a rapid fall in the B.S.R. and disappearance of friction a week later.

The dose was again reduced after eleven weeks, causing the blood level to fall to 8 mg. per 100 c.cm. Again friction recurred, this time unaccompanied by a rise in the B.S.R. With an increase in dosage, friction again disappeared. Therapy was continued until the end of the sixteenth week. At the eighteenth week mobilization was followed by a sharp increase in the B.S.R. unaccompanied by any symptoms. The administration of 300 gr. of salicylate again caused a rapid fall in the B.S.R., although a steady fall in salicylate level was observed, an example of tolerance commonly seen in cases receiving salicylates for long periods.

The case is summarized in Fig. 3.

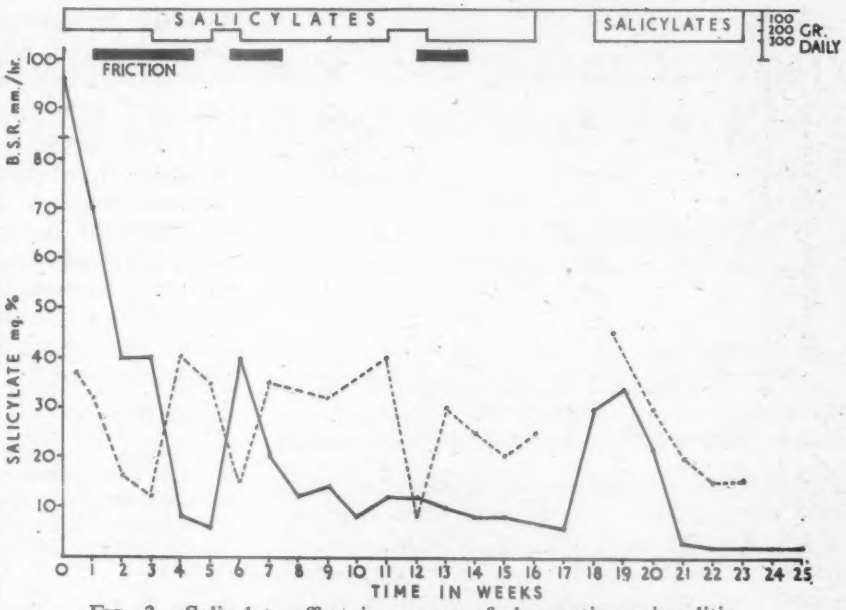


FIG. 3.—Salicylate effect in a case of rheumatic pericarditis.

### Other Observations

A few general observations may be made here. Salicylate is most effective when commenced early in the disease, and if administration is delayed for several weeks less dramatic effects are obtained. The drug appears to become less and less effective in the treatment of polycyclic relapses. A low-grade type of infection with a subacute arthritis and low B.S.R., and without carditis verging on the rheumatoid type, was seen in this series in four cases, three in women, and appeared resistant to therapy in moderate dosage.

### Toxic Effects

The beneficial effects of massive salicylate therapy must be weighed against possible toxic effects. These have recently been reviewed by Graham and

TABLE 2
EFFECTS OF SALICYLATE THERAPY ON CARDITIS

| | Coburn (1943) | | Manchester (1946) | | | Warren and others (1946) | | | Keith and Ross (1945) | | Present series | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. cases | % V.D. | No. cases | % V.D. | % P.H.D. | No. cases | % V.D. | % P.H.D. | No. cases | % V.D. | No. cases | % V.D. | % P.H.D. |
| Small dosage | 63 | 31·9 | 48 | 13 | 3·9 | 98 | 4·1 | 4·1 | 29 | 10·3 | 25 | 8 | 25 |
| Moderate ,, | — | — | — | — | — | — | — | — | — | — | 29 | 17·2 | 14·1 |
| Massive ,, | 38 | nil | 71 | 7·4 | 13 | 88 | 3·4 | 3·1 | 57 | 8·8 | 21 | nil | 8·5 |

V.D.=Permanent valvular damage. P.H.D.=Potential heart disease.

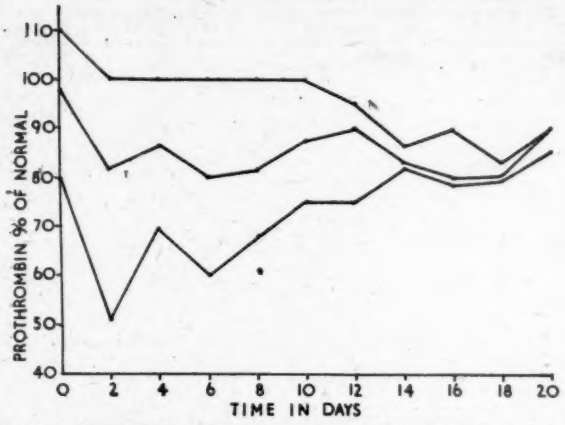


FIG. 4.—Salicylate effect on prothrombin concentration.

Parker (1948). These workers divided toxic effects into three groups. In the first were symptoms which are common but unimportant—tinnitus, headache, nausea, sweating, and transient vomiting —and which can be taken as an indication that the plasma level is approaching a therapeutic concentration. In the second group were symptoms which are uncommon and which individually may be serious—such as vertigo, drowsiness, mental upsets, and haemorrhage. In the third group were symptoms both common and alarming, namely severe vomiting and hyperventilation. The appearance of symptoms in the last two groups call for an immediate modification of the dose employed. Severe vomiting was seen in the present series on two occasions and marked hyperpnoea on five.

The risk of haemorrhage due to hypoprothrombinaemia was a much-feared complication of salicylate therapy. Since it was shown by Link and his co-workers (1943) that salicylic acid produced hypoprothrombinaemia in rats, which could be prevented by the addition of vitamin K, several reports of death due to haemorrhage in salicylate therapy have been reported (Troll and Menten, 1945 ; Graham and Parker, 1948). A study of five cases receiving massive salicylate therapy was made, prothrombin times by Quick's method being performed twice daily. A fall in the prothrombin concentration was produced which tended to become normal later. In no case did the level fall below 50 per cent. of a normal control (Fig. 4). As it has been shown that the prothrombin must be reduced to a fifth of normal before haemorrhage is likely to occur, no adequate safety margin existed. The addition of vitamin K in a dosage of 1 mg. per g. of salicylate daily will neutralize the haemorrhagic tendency (Shapiro, 1944). Vitamin K in doses of 10 mg. daily was given as a routine in cases on massive therapy ; no cases of spontaneous haemorrhage occurred. Haemorrhage must, therefore, be considered as a rarity in the dosage commonly employed.

**Summary**

In the present survey eighty Service patients suffering from rheumatic fever were treated by minimal, moderate, and massive doses of salicylates. A significant reduction in the period of fever, arthralgia, and active infection was demonstrated in the group receiving massive therapy. No reduction in the relapse rate or in the incidence of carditis was seen. The dosage is discussed, and possible toxic effects considered.

My thanks are due to the Director General of Medical Services, Royal Air Force, for permission to publish this paper, to the R.A.F. consultants in medicine, Sir Alan Rook, Sir John Conybeare, and Group Captain Rumball for their encouragement and advice, and to my colleagues F/Lts. B. R. Hillis, E. R. Ellis, and E. A. Harris, without whom this work would not have been possible.

REFERENCES

Brodie, B. B., Udenfriend, S., and Coburn, A. F. (1944). *J. Pharmacol.*, **80**, 114.
Coburn, A. F. (1943). *Bull. Johns Hopk. Hosp.*, **73**, 435.
Graham, J. D. P., and Parker, W. A. (1948). *Quart. J. Med.*, **17**, 153.
Homburger, F. (1946). *Amer. J. med. Sci.*, **211**, 346.
Harris, T. N. (1947). *Ibid.*, **213**, 482.
Jones, T. D. (1944). *J. Amer. med. Ass.*, **126**, 481.
Lees, D. B. (1903). *Brit. med. J.*, **2**, 1318.
Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D. (1943). *J. Biol. Chem.*, **147**, 463.
Maggioni, G. F. (1948). *Arch. Dis. Childh.*, **23**, 40.
Manchester, R. C. (1946). *Arch. int. Med.*, **77**, 317.
—— (1946). *Ibid.*, **78**, 170.
—— (1946). *J. Amer. med. Ass.*, **131**, 209.
Parker, W. A. (1948). *Quart. J. Med.*, **17**, 229.
Quick, A. J. (1942). " The Haemorrhagic Diseases and Physiology of Haemostasis ". Charles C. Thomas. Springfield, Illinois.
Raporport, S., and Guest, G. M. (1946). *Proc. Soc. exp. Biol. N.Y.*, **61**, 43.
Shapiro, S. (1944). *J. Amer. med. Ass.*, **125**, 546.
Stricker, ??. (1876). *Berl. klin. Wschr.*, **13**, 1, 15, 99.
Taran, L. M., and Jacobs, M. H. (1945). *J. Paediat.*, **27**, 59.
Troll, M. M., and Menten, M. L. (1945). *Amer. J. Dis. Child.*, **69**, 37.
Warren, H. A., Higley, C. S., and Coombs, F. S. (1946). *Amer. Heart J.*, **32**, 311.

**Traitement du Rhumatisme Articulaire aigu par des Doses Massives de Salicylate**

RÉSUMÉ

Au cours de l'étude ci-dessus quatre-vingt malades provenant de l'Armée ont été traités par des doses faibles, modérées, et massives de salicylate. Le groupe recevant des doses massives a présenté une diminution marquée de la durée de la fièvre, de l'arthralgie, et de l'infection active. On n'a constaté aucune diminution du nombre des rechutes ni de la fréquence de l'atteinte cardiaque. L'auteur discute la posologie et examine la possibilité d'accidents toxiques.

# THIOURACIL ADMINISTRATION AND THYROIDECTOMY IN EXPERIMENTAL POLYARTHRITIS OF RATS*

BY

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Many clinical reporters have alluded to the possible influence of the functional state of the thyroid gland in rheumatic disease. Several have reported the coincidence of hyperthyroidism and rheumatoid arthritis (Snorrason, 1943 ; Duncan, 1928, 1932 ; Garrod, 1906 ; Jones, 1909 ; Spriggs, 1908 ; Thiroloix and others, 1926; Bauer and others, 1940), the coincidence of rheumatic fever and hyperthyroidism (Schiødt, 1943), and relationship of thyroid hypofunction to degenerative joint disease or osteo-arthritis (Hall and Monroe, 1932-3; Falcone and Delbene, 1945). Some have observed that the basal metabolism is increased more often in rheumatoid arthritis than in degenerative joint disease or mixed arthritis (Rawls and others, 1938). Others have doubted that thyroid dysfunction had any marked influence on arthritis in general (Bauer, 1939; Pemberton and Tompkins, 1920; Freyberg, 1942). Patients have been observed to develop a clinical picture resembling rheumatoid arthritis following thyroidectomy (Monroe, 1935). Hypertrophic pulmonary osteo-arthropathy after thyroidectomy has been previously reported (Cushing, 1937 ; Rynearson and Sacasa, 1941).

Accordingly there seems to be considerable clinical evidence and continued suspicion that the thyroid gland is in some way implicated in arthritis. Therefore it seemed desirable to us to determine whether thyroidectomy had an influence on the course of experimental polyarthritis and whether such changes were due to lowering of the basal metabolic rate or to ablation of the gland itself. No previous effort has been made to determine the influence of the thyroid on the course of experimental arthritis of any kind. Polyarthritis in rats and mice has been used in recent years as a method of evaluating chemotherapeutic agents (Collier,

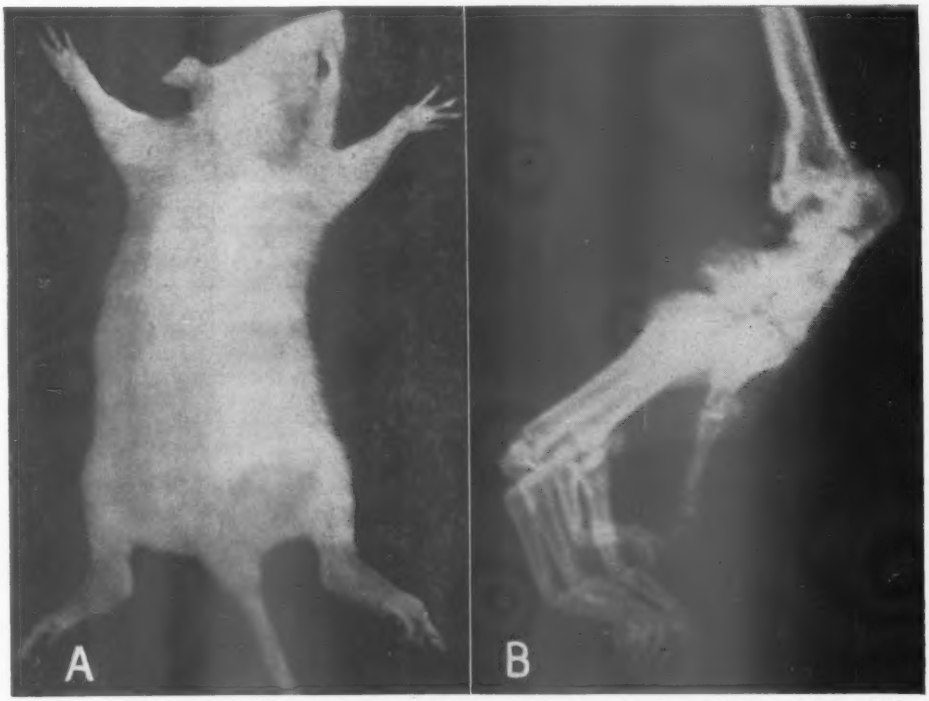


FIG. 1.—Albino rat showing (A) polyarthritis two weeks after intraperitoneal inoculation of 2 c.cm. broth culture of L4 strain of pleuropneumonia-like organisms, and (B) radiograph showing arthrodesis of tarsal joints two months after inoculation.

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† With the technical assistance of Jacqueline C. Landale, Pelagio S. Tabar, and Selig A. Gellert.

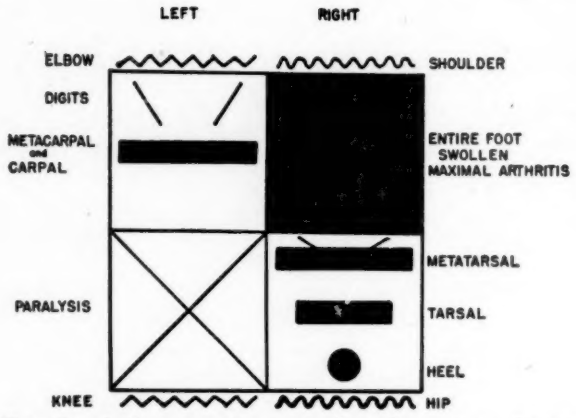


FIG. 2.—Arthrogram for recording the extent of joint involvement in experimental polyarthritis of rats.

1939 a and b; Findlay and others, 1939 and 1940; Sabin and Warren, 1940a and b, 1941; Sabin and Morgan, 1940; Snow and Hines, 1941; Sabin, 1942; Preston and others, 1942; Powell and Rice, 1944; Powell and others, 1946; Browning and Rice, 1947; Tripi and Kuzell, 1947). While the pathological picture is not the same as that in rheumatoid arthritis in man, the experimental arthritis produced by the L4 strain of pleuropneumonia-like organisms in rats and mice is amenable to chrysotherapy. Fig. 1 shows a rat with arthritis produced by the intraperitoneal inoculation of 2 c.cm. of a broth culture of the L4 strain, of pleuropneumonia-like organisms. This experimental arthritis is, at present, the procedure of choice for the study of factors which may influence the course of joint disease. Our objective was to determine whether reduction of the metabolic rate by prolonged administration of thiouracil, or by thyroidectomy, would alter the incidence and severity of rat polyarthritis due to pleuropneumonia-like organisms of the L4 strain (P.L.O.)*. This paper presents the results obtained.

## Methods

Albino rats were used throughout and, whenever possible, the numbers of males and females were equal. All unmedicated animals were allowed to eat ground purina dog chow checkers† (basic diet) and to drink water freely.

The experimental polyarthritis was produced by inoculating each animal, intraperitoneally, with 2 c.cm. of an 18- to 24-hour culture of P.L.O. The microbes were grown as a routine on agar or in broth media consisting of a buffered yeast-extract-tryptose base enriched with 10 per cent. of Seitz-filtered horse serum to which 2 per cent. of agar was added for the solid medium (Tripi and Kuzell, 1947). Before inoculation all animals were weighed once weekly, and after inoculation the weighing schedule coincided with the examination of the animals for arthritis. Food consumption was recorded at least twice weekly (usually three times), and daily during the week following inoculation.

* Abbreviation of pleuropneumonia-like organisms of the L4 strain used throughout this paper.

† Purina dog chow checkers are compressed pellets containing: protein 21 per cent., fat 4 per cent., fibre 6 per cent., nitrogen-free extract 46 per cent., and ash 9 per cent.

TABLE 1

SCORE EVALUATION ACCORDING TO DEGREE AND EXTENT OF RAT POLYARTHRITIS FOR EACH EXTREMITY

| Score | Degree | Extent of arthritic involvement |
|---|---|---|
| 0 | None | None. |
| 1 | Minimal | Swelling only in toe joints, or transitory swelling of any single joint, or lasting weakness of an extremity with the involved joint, or joints, undetermined. |
| 2 | Moderate | Swelling of 4, or more, toe joints, or severe and lasting involvement of a single large joint, or several small joints, or paralysis of a foot due to involvement of the wrist or heel without swelling. |
| 3 | Severe | Extensive, and lasting, involvement of several joints (maximal for the anterior extremities) followed by ankylosis. |
| 4 | Severest | Extensive involvement of joints in all regions of a foot with extreme swelling of an entire foot followed by ankylosis. In the anterior extremities, maximal involvement plus involvement of the elbow or shoulder. |
| 5 | Severest | Same as Score 4 plus involvement of the knee or hip. |

During the week following inoculation the animals were examined daily for symptoms of joint involvement, on alternate days during the second week, twice during the third week, and once weekly thereafter. At each examination, a diagrammatic record (arthrogram, Fig. 2) of the location and degree of involvement of affected joints of the extremities was made according to a slight modification of the method of Sabin and Warren (1940b).

At the end of an experiment, all arthrograms for each rat were compiled into a single composite arthrogram which was given a numerical score according to the recorded number of affected joints and the degree to which they were involved. The score values ranged from 0 to 4 for each anterior extremity and from 0 to 5 for each posterior extremity ; thus the arthrogram score for any individual rat lay within a range of 0 to 18, 0 indicating no demonstrable signs of arthritis, and 18 indicating that all four extremities were involved to a maximum degree (Table 1). This method of scoring was purely arbitrary, being intended as a rough quantitative clinical estimation of the macroscopic joint involvement. There was little difficulty in scoring minimal and maximal degrees of arthritis, but between these extremes the score depended largely on the judgment of the observer.

At death, or when experiments were terminated after 4 to 6 months, all animals underwent autopsy examination. All lesions found were examined bacteriologically, whether they were in the joints or the viscera. Animals which had shown joint involvement were radiographed to demonstrate the extent of arthritic changes.

The effects of thiouracil on experimental polyarthritis were observed in rats weighing approximately 100 g. Thiouracil was used in a concentration of 0·1 per cent. incorporated into the basic ground diet by mixing for 30 minutes with a mechanical mixer. Unmedicated controls received the basic diet. At the end of five, seven, and twelve weeks, groups of rats on the thiouracil diet, with their respective controls, were inoculated with P.L.O. In the *first* and *second* series, inoculated after five to seven weeks respectively, half the animals were changed to the basic diet at the time of inoculation. A group of controls equivalent in weight to the thiouracil-animals was also inoculated. Since the results subsequently obtained did not warrant continuation of these procedures, all animals of the third series were kept on the thiouracil diet after being inoculated at the end of twelve weeks. No inoculation-weight controls were used. Forty rats receiving the thiouracil were not inoculated and served as a control group for comparison with the uninoculated unmedicated controls, all inoculated animals, and those removed from the thiouracil diet at the time of inoculation with P.L.O.

Thyroidectomies were performed on a group of thirty rats for comparison regarding the degree of hypothyroidism caused by the prolonged administration of thiouracil. Both the thyroidectomized animals and their controls with thyroids intact received the basic diet supplemented with milk in order to overcome calcium imbalance caused by unavoidable removal of the parathyroids along with thyroid gland. Groups of thyroidectomized animals were inoculated twenty-five, seventy, and eighty-six days after operation.

Periodically, the oxygen consumption of normal, thyroidectomized, thiouracil-medicated, arthritic-thiouracil-medicated, and arthritic rats was determined according to the procedure of Tainter and Rytand (1934). Surface area was calculated according to the formula S. A. $= 9{\cdot}1 \times W^{2/3}$, after Benedict (1934).

Blood was examined in rats on thiouracil and their controls. Care was used to prevent excitation of the animals while blood was being taken. Once weekly, from the beginning of an experiment and during a period of seventy-two days, total leucocyte and differential leucocyte counts were made on the blood of animals in the first two groups and their respective controls selected at random from each group, but this was done infrequently since all values obtained were normal.

Toxic agents, chemically and physically different from thiouracil, were administered in order to determine whether toxicity in general had any effect on the development of arthritis in rats inoculated with P.L.O. This was done to aid in evaluating any possible specific toxic effects of thiouracil in enhancing this type of experimental arthritis. The following drugs were used : phenobarbital sodium, 0·1 per cent. in the basic diet (Hanzlik and Laqueur, 1946), arsenic trioxide, 0·01 per cent. in drinking water (Lehman and Chase, 1944). On the fourteenth day of medication all animals were inoculated with P.L.O.

The details of all changes were summarized in tables or curves for comparison ; however, most of these have been omitted here since minor differences revealed nothing significant with respect to the principal objective, or fell within range of variations in the different groups of animals. The most important result obtained, the increased severity of the polyarthritis caused by the thiouracil, may now be discussed.

### Changes in Joints of Polyarthritic Thiouracil-Medicated and Thyroidectomized Rats

**Thiouracil-Medicated Rats.**—A numerical representation of the degree of joint involvement of inoculated and thiouracil-treated rats and their controls is shown in Table 2, and the percentage incidence of arthritis and deaths among these animals in Table 3. It is evident that the incidence and degree of arthritis in animals inoculated with P.L.O. after thiouracil medication for thirty-four to fifty-one days was not significantly different from that of the controls. Polyarthritis failed to develop in many of these animals. The greatest degree of arthritis involvement was obtained with the combination of continued thiouracil administration and inoculation of the animals after eighty-five days of thiouracil medication, but the mortality was somewhat greater among these animals, 18 per cent. as compared with 13 per cent. in rats inoculated after fifty-one days on thiouracil. All the thiouracil animals became

TABLE 2

COMPOSITE ARTHROGRAM SCORES FOR THIOURACIL MEDICATED AND CONTROL RATS FOLLOWING INOCULATION WITH PLEUROPNEUMONIA-LIKE ORGANISMS (L4 STRAIN)

| | P.L.O.* alone (controls) | | Continued thiouracil† with P.L.O.* | | P.L.O.* preceded by thiouracil | |
|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | Males | Females |
| | | | | | 34 days of thiouracil | |
| No. of rats | 10 | 10 | 8 | 8 | 7 | 7 |
| Per cent. dead | 0 | 10 | 25 | 50 | 57 | 87 |
| Composite arthrogram score | 5·3 | 4·9 | 3·1 | 5·0 | 3·6 | 2·2 |
| | | | | | 51 days of thiouracil | |
| No. of rats | 6 | 10 | 6 | 10 | 10 | 10 |
| Per cent. dead | 0 | 20 | 17 | 10 | 0 | 0 |
| Composite arthrogram score | 4·4 | 3·3 | 3·2 | 3·7 | 3·8 | 3·6 |
| | | | | | 85 days of thiouracil | |
| No. of rats | 15 | 15 | 17 | 17 | — | — |
| Per cent. dead | 7 | 13 | 12 | 24 | — | — |
| Composite arthrogram score | 4·0 | 3·6 | 8·0 | 5·0 | — | — |

* Inoculation with pleuropneumonia-like organisms (L4 strain).
† For variable periods up to 233 days (see text).

TABLE 3

PERCENTAGE INCIDENCE OF ARTHRITIS AND DEATHS AMONG THIOURACIL-TREATED AND UNTREATED RATS FOLLOWING P.L.O.* INFECTION

| Experimental groups | Incidence of arthritis (%) | Deaths | | | |
|---|---|---|---|---|---|
| | | Total (%) | Early (within 4 days) (%) | Late (infected non-arthritic) (%) | Late (arthritic) (%) |
| *Group* 1, P.L.O.* inoculated after 34 days of thiouracil : | | | | | |
| (1) No thiouracil | 100 | 5 | 0 | 0 | 5 |
| (2) Thiouracil continued throughout | 60 | 38 | 25 | 13 | 0 |
| (3) Thiouracil discontinued after P.L.O. | 65 | 71 | 7 | 29 | 35 |
| *Group* 2, all inoculated* at 51 days thiouracil : | | | | | |
| (1) No thiouracil | 100 | 13 | 0 | 0 | 13 |
| (2) Thiouracil continued throughout | 81 | 13 | 0 | 13 | 0 |
| (3) Thiouracil discontinued after P.L.O.* | 100 | 0 | 0 | 0 | 0 |
| *Group* 3, all inoculated* at 85 days thiouracil: | | | | | |
| (1) No thiouracil | 97 | 10 | 0 | 3 | 7 |
| (2) Thiouracil continued throughout | 100 | 18 | 0 | 0 | 18 |

* Inoculation with pleuropneumonia-like organisms (L4 strain).

TABLE 4

INCIDENCE AND SEVERITY OF ARTHRITIS AND PERCENTAGE OF DEATHS AMONG INOCULATED RATS AFTER CONTINUED ADMINISTRATION OF ISOPROPYL ALCOHOL PHENOBARBITAL AND ARSENIC TRIOXIDE

| Drug | Mortality before inoculation (%) | Mortality after inoculation (P.L.O.)* | | | | Incidence of arthritis (%) | Composite arthrogram score |
|---|---|---|---|---|---|---|---|
| | | Total (%) | Early (infected < 4 days) (%) | Late (infected non-arthritic) (%) | Late (infected arthritic) (%) | | |
| Unmedicated controls .. | 0 | 45 | 10 | 0 | 35 | 100 | 4·9 |
| Isopropyl alcohol .. | 40 | 50 | 0 | 17 | 33 | 75 | 3·6 |
| Phenobarbital sodium .. | 50 | 40 | 0 | 0 | 40 | 100 | 4·9 |
| Arsenic trioxide .. | 15 | 18 | 0 | 0 | 18 | 88 | 5·2 |

* Pleuropneumonia-like organisms (L4 strain).

arthritic, and there was a significant increase in the degree of joint involvement among these animals as compared with their controls.

There was a greater mortality among all thiouracil-treated rats than among the controls, the mortality being highest among those inoculated after five weeks. Among these latter rats the percentage of deaths was greater among the animals removed from the thiouracil diet to the control diet at the time of inoculation, and was further increased for the females as compared with the corresponding males. The reason for the increased mortality among the treated animals inoculated after five weeks was considered not to be due to greater virulence of the culture used for inoculation of the rats, but rather to increased susceptibility of the host to the microbes (a false enhancement of the virulence of the culture) brought about by the disturbed metabolism of the rats. In all groups, animals which died within the first few days after inoculation were usually free of joint swellings, the cause of death being invariably peritonitis. The rats which died later exhibited joint swellings, but the cause of death was presumably due to overwhelming infection manifested by the widespread distribution of small abdominal abscesses and, less often, pulmonary abscesses. The distribution and size of the abscesses was dependent upon the length of time which had elapsed since inoculation. Sixty per cent. of the animals sacrificed at the end of the experimental period exhibited such abscesses, and in most instances the lesions were hard and large, often 1 to 2 cm. in diameter, and heavily encapsulated ; and the grey-white, friable material within the capsule yielded pure cultures of P.L.O. The microbes were recovered at autopsy from the brain, lungs, spleen, liver, abdominal abscesses, testes, and prostate gland of two animals. It was possible invariably to recover regularly the microbes from the peritoneal exudate four days after inoculation ; they were recovered from ankylosed joints in three rats five months after inoculation. Animals which had received thiouracil showed the same lesions as the unmedicated animals, but approximately 80 per cent. of these had gross visceral lesions at autopsy. Thus, in general, the suggested greater severity of the polyarthritis during the life of thiouracil-medicated rats was also manifested by the presence of more severe and extensive pathological lesions at autopsy.

**Thyroidectomized Rats.**—Neither the rates of growth nor food consumption of thyroidectomized rats differed significantly from those of the controls. Leucocyte counts were not made prior to thyroidectomy, but counts done at intervals following thyroidectomy and inoculation did not differ in any significant respect from those of the controls.

There were no deaths among thirty thyroidectomized animals inoculated with P.L.O., at 25, 70, and 86 days after thyroidectomy. The incidence of arthritis among control animals was 100 per cent., and among thyroidectomized animals 95 per cent. The averages of the arthrogram scores for control and thyroidectomized males were practically the

same, i.e. 3·2 ; for the female controls the average was 3·8, and for the thyroidectomized females 3·6. Therefore, lack of thyroid function could not have been responsible for the suggested increase in severity of the polyarthritis produced by thiouracil.

**Other Toxic Agents.**—The arthrogram scores, per cent. mortality, and incidence of arthritis in inoculated rats after continued administration of phenobarbital (fourteen weeks), isopropyl alcohol (fourteen weeks), and arsenic trioxide (four weeks) are shown in Table 4. The estimated average daily doses of these drugs for each rat were as follows: 0·05 c.cm. (males) and 0·03 c.cm. (females) of isopropyl alcohol, 2·0 mg. (males) and 1·4 mg. (females) of arsenic trioxide, and 15·0 mg. (males) and 10·0 mg. (females) of phenobarbitone.

It is seen that the incidence and severity of the arthritis among these three groups of medicated animals inoculated with P.L.O. was generally not greater than that for the unmedicated controls. In fact mortality was appreciably less in rats receiving isopropyl alcohol (75 per cent.) and arsenic trioxide (88 per cent.). The mortality before inoculation among animals receiving isopropyl alcohol and phenobarbital alone, 40 and 50 per cent. respectively, suggested the possibly greater toxicity of these compounds as compared with thiouracil alone (2 per cent.). The uniform, though generally depressed, rate of gain in weight for animals receiving isopropyl alcohol, phenobarbital, and arsenic trioxide was in marked contrast to the early normal rate of gain which became abruptly levelled off and was followed by a minimal rate of gain as in thiouracil-poisoned animals. Besides reduction of body weight there were also some decreases in food consumption and some mortality in all three groups, in confirmation of previous investigations of isopropyl alcohol by Lehman and Chase (1944), of arsenic trioxide by Sollmann (1921), and of phenobarbitone by Hanzlik and Laqueur (1946). Since the chronic toxicity of these physically and chemically different drugs did not increase the severity of the experimental polyarthritis, even though they appeared to be more toxic than thiouracil, the thiouracil medication seemed to predispose to greater severity of the arthritis in some peculiar way. Our results with inoculated rats medicated with isopropyl alcohol, arsenic, and phenobarbital are somewhat vitiated by the fact that fewer animals of these groups survived for comparable determination of the incidence of arthritis among those on thiouracil. At least it can be said that the numbers of rats on these drugs were considerable, yet their toxic actions did not seem to increase the severity of the arthritis.

### Other Changes in Thiouracil-Medicated and Inoculated Rats

Changes in body weight, leucocyte counts, differential counts, and food consumption in inoculated unmedicated controls and in thiouracil-medicated and inoculated (P.L.O.) rats were practically the same. There were temporary fluctuations in these functions and elements, often decreases, if anything, at the beginning of an experiment, followed by recoveries to pre-medication, or pre-inoculation, levels on the fourth day. From there on to the conclusion of the experiments any changes were minor or insignificant except for growth, which generally increased in all animals. The somewhat greater loss of body weight in thiouracil-medicated and inoculated rats was probably due to decreased food consumption, since they ate about 10 per cent. less food during this time. There is no good reason to believe that these temporary and often comparatively minor changes contributed significantly to the increased severity of the polyarthritis under thiouracil. This suggested that the increased severity of the arthritis was the result of some intrinsic systemic action of the thiouracil.

As might be expected the basal metabolic rate of the fourteen thiouracil-medicated rats was reduced to 58 per cent. of the basal metabolic rate of forty uninoculated unmedicated rats. The metabolic rate was reduced by the same amount in twenty thyroidectomized rats and twenty arthritic, thiouracil-medicated rats, but it was about 80 per cent. of normal in six unmedicated arthritic rats. Neither sex nor age of these rats influenced the basal metabolic rate.

The thyroid glands of rats which had received thiouracil for 233 days, with or without P.L.O., showed about a 500 per cent. increase in weight, with a tendency to slightly lower weights in those rats on thiouracil and P.L.O. No significant sex difference in the average per cent. weights of thyroids of normal or medicated rats was observed. Histologically, the thyroids of rats inoculated with P.L.O. only were normal ; whereas those of thiouracil-medicated rats were diffusely hyperplastic, devoid of colloid, and after prolonged thiouracil medication showed nodular hyperplasia dependent in degree on the duration of medication (Kuzell and others, 1948). The relationship of size and extent of histological changes in the thyroid to duration of thiouracil medication is supported by the results of several investigators, chiefly by those using periods up to a hundred days, and by one or two others using periods of 205 days or longer where the relative size of the gland was 350 per cent.

(females) and 500 per cent. (males) (Thyssen, 1947), an order of magnitude confirmed by us. Clearly our rats responded typically to thiouracil. A separate report on the endocrines of the rats in this study is to be made by Dr. G. L. Laqueur of the department of pathology in this university.

### Summary and Conclusions

1. Albino rats receiving thiouracil in the diet for periods from 120 to 233 days developed hyperplastic thyroids with nodular hyperplasia. When infected at the end of eighty-five days of such medication with the L4 strain of pleuropneumonia-like organisms these animals developed a suggestively greater severity of polyarthritis than did the controls, and showed greater mortality.

2. Thyroidectomized albino rats which had an average basal metabolic rate of only 58 per cent. of normal (the same as for the thiouracil-medicated rats), when infected with the L4 strain of pleuropneumonia-like organisms developed polyarthritis which was the same as that of the controls. Presumably, therefore, lack of thyroid does not affect the course of this polyarthritis.

3. Albino rats poisoned with agents chemically and physically different from thiouracil, namely, arsenic trioxide, isopropyl alcohol, and phenobarbital, showed no increase in severity of polyarthritis due to the L4 strain of pleuropneumonia-like organisms.

4. Thus the suggested increase in severity of this experimental polyarthritis in thiouracil-medicated animals for the largest period (eighty-five days) is believed to be due to some peculiar intrinsic action of the thiouracil.

### References

Bauer, W. (1939). *New Engl. J. Med.*, **221**, 524.
——, Ropes, M. W., and Waine, H. (1940). *Physiol. Rev.*, **20**, 272.
Benedict, F. G. (1934). *Ergeb. der Physiol.*, **36**, 300.
Browning, J. M., and Rice, R. M. (1947). *Proc. Amer. Fed. Clin. Res.*, **3**, 7.
Collier, W. A. (1939a). *Z. Immunitäts.*, **95**, 132.
—— (1939b). *Geneesk. Tijdschr. Nedrl.-Indie*, **79**, 796.
——, and Staverman, G. J. (1940). *Annals of the Rheumatic Diseases*, **2**, 58.
Cushing, E. H. (1937). *Internat. Clin.*, **2**, 200.
Duncan, W. S. (1928). *J. Amer. med. Ass.*, **91**, 1779.
—— (1932). *Ibid.*, **99**, 1239.
Falcone, A., and Delbene, R. (1945). *Bol. Liga Urug. Contra el Reumat.*, **1**, 246.
Findlay, G. M., Mackenzie, R. D., MacCallum, F. O., and Klieneberger, E. (1939). *Lancet*, **2**, 7.
——, ——, —— (1940). *Brit. J. exp. Path.*, **21**, 13.
Freyberg, R. H. (1942). *J. Amer. med. Ass.*, **119**, 1165.
Garrod, A. E. (1906). *Trans. Med. Soc. London*, **29**, 94.
Hall, F. C., and Monroe, R. T. (1932-3). *J. Lab. clin. Med.*, **18**, 439.
Hanzlik, P. J., and Laqueur, G. L. (1946). *Stanford med. Bull.*, **4**, 21.
Jones, R. L. (1909). *Lancet*, **1**, 192.
Kuzell, W. C., Tripi, H. B., Gardner, G. M., and Laqueur, G. L. (1948). *Science*, **107**, 374.
Lehman, A. J., and Chase, H. F. (1944). *J. Lab. clin. med.*, **29**, 561.
Monroe, R. T. (1935). *New Engl. J. Med.*, **212**, 1074.
Pemberton, R., and Tompkins, E. H. (1920). *Arch. int. Med.*, **25**, 241.
Powell, H. M., Jamieson, W. A., and Rice, R. M. (1946). *Proc. Soc. exp. Biol. N.Y.*, **62**, 8.
——, and Rice, R. M. (1944). *J. Lab. clin. Med.*, **29**, 372.
Preston, W. S., Block, W. D., and Freyberg, R. H. (1942). *Proc. Soc. exp. Biol. N.Y.*, **50**, 253
Rawls, W. B., Ressa, A. A., Gruskin, B., and Gordon, A. S. (1938). *Ann. int. Med.*, **11**, 1401.
Rynearson, E. H., and Sacasa, C. F. (1941). *Proc. Mayo Clin.*, **16**, 353.
Sabin, A. B. (1942). *Ibid.*, **17**, 542.
——, and Morgan, I. M. (1940). *Arch. Path.*, **29**, 735.
——, and Warren, J. (1940a). *Science*, **92**, 535.
——, —— (1940b). *J. Bact.*, **40**, 823.
——, —— (1941). *J. Amer. med. Ass.*, **117**, 1561.
Schiødt, E. (1943). *Nord. Med.* (*Hospitalstid*), **20**, 1787.
Snorrason, E. (1943). *Acta med. scand.*, **113**, 329.
Snow, J. E., and Hines, H. M. (1941). *Proc. Soc. exp. Biol. N.Y.*, **46**, 257.
Sollmann, T. (1921). *J. Pharm. exp. Therap.*, **18**, 43.
Spriggs, E. I. (1908). *Lancet*, **2**, 1877.
Tainter, M. L., and Rytand, D. A. (1934). *Proc. Soc. exp. Biol. N.Y.*, **32**, 361.
Thiroloix, J., and others (1926). *Bull. Mém. Soc. méd. Hôp. Paris*, **50**, 1033.
Thyssen, J. (1947). *Acta Pharmacol. Toxicol.*, **3** (Supl. 2).
Tripi, H. B., and Kuzell, W. C. (1947). *Stanford Med. Bull.*, **5**, 98.

### Administration de Thiouracile et Thyroïdectomie dans la Polyarthrite expérimentale chez le Rat

#### Résumé et Conclusions

1. Des rats blancs recevant du thiouracile dans leur alimentation pendant 120 à 233 jours, ont présenté une hyperplasie thyroïdienne nodulaire. Lorsque ces animaux avaient été infectés après 85 jours de ce traitement par une souche L4 de microbes du type pleuropneumonique, ils ont présenté une polyarthrite dont la gravité était nettement plus grande que chez les animaux témoins, et leur mortalité était plus élevée.

2. Des rats blancs thyroïdectomisés dont le métabolisme basal était en moyenne 58 pour cent de la normale (le même que chez les rats traités au thiouracile), inoculés avec la souche L4 de microbes du type pleuropneumonique ont présenté une polyarthrite semblable à celle des témoins. L'absence de thyroïde ne semble donc pas affecter l'évolution de cette polyarthrite.

3. Des rats blancs traités par des substances toxiques différentes du thiouracile aux points de vue chimique et physique, tels que l'anhydride arsénieux, l'alcool isopropylique, et le gardénal, n'ont présenté aucune augmentation de la gravité de la polyarthrite provoquée par la souche L4 de microbes du type pleuropneumonique.

4. Il est donc probable que la gravité acrue de cette polyarthrite expérimentale chez des animaux recevant du thiouracile pour le période la plus longue (quatre-vingt-cinq jours) est due à une action particulière du thiouracile.

# COMPARATIVE RESULTS OF COPPER SALTS AND GOLD SALTS IN RHEUMATOID ARTHRITIS

BY

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Twenty years' experience has established the value of gold salts in the treatment of rheumatoid arthritis and allied conditions. Six years ago the present author began to try out copper compounds as a complement, and the use of one or the other of these metals has improved our therapeutic results.

### Chrysotherapy

The following schedules of treatment have been established over the past fifteen years :

1. The series of injections should consist of small or moderate doses of 0·05, 0·1, 0·2 g. (for gold salts), given at intervals of from five to seven days, mostly by the intramuscular route.

2. The total amount of gold salts for one series should not be less than 1 g. or more than 1·5 g. (average 1·2 g.).

3. The intervals between each series should not exceed six weeks between the first two series, and two, three, or four months between the others, the spacing depending upon the condition of the patient.

4. The treatment should be continued for months or even years as long as the arthritis is advancing and the sedimentation rate is high. It should not be decided to end treatment as long as one of these conditions remains.

5. When treatment has been completed the condition of the patient and the sedimentation rate should be tested every three months in the first year and every six months in the two following years. If articular involvement reappears, or if the sedimentation rate rises (even with no symptoms), treatment should be resumed immediately.

This scheme is essentially different from that of some American authors, who give minimal doses without any interruption over very prolonged periods, and from that of K. Secher, who injects progressively increasing doses, up to 0·5 or 1 g., until a skin reaction is produced.

### Copper Therapy

The introduction of copper salts has not fundamentally altered the above principles, but the author has adapted them to the special qualities of these compounds.

Since 1942 the author has used the intravenous route for sodium-meta-(allylcuprothiocarbamido)-benzoate (Cupralene : 19·85 per cent. copper), with a dosage of 0·25 to 0·50 g. for each injection given twice a week, and a total of 2·50 to 5 g. for each series. Since 1945 the author has also used by the intramuscular or intravenous route diethylamine-(cupro-oxyquinoleum)-sulphonate (Dicuprene 6·5 per cent. copper), at a dose of 0·5 g. two or three times a week, with a total dosage of 6 to 9 or 12 g. for each series. Intervals between the series of copper injections should not exceed two months as a rule, since the excretion of these salts is quicker than that of gold salts.

### Comparative Results of Copper Therapy and Chrysotherapy

In the treatment of a chronic group of diseases such as rheumatoid arthritis the assessment of the clinical results is of value only if it covers a prolonged period—at least two years, and if possible more. It is well known that progress is not continuous but subject to partial remissions. The importance of spontaneous remissions has, however, been greatly exaggerated by many authors, especially in the United States. Such remissions generally consist in functional improvement, with persistence of clinical signs, and they never last very long. For these reasons, and owing to the length of time necessary for useful observations, control cases are often of little value, since conditions vary from case to case.

We have limited our statistical studies to a few cases observed for over two years, and these have appeared to confirm our clinical impressions. From the Tables, which deal exclusively with true rheumatoid cases, we can draw the following conclusions :

1. In early cases, below one year's duration (Table 1), copper salts (particularly Cupralene) given by the intravenous route give better results

TABLE 1

EARLY CASES (LESS THAN A YEAR'S DURATION)

| Treatment | Cases | Very good | | Good | | Medium | | Failures | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % |
| Gold .. .. | 8 | 4 | 50 | 2 | 25 | 1 | 12·5 | 1 | 12·5 |
| Cupralene .. | 12 | 5 | 41·7 | 7 | 58·3 | 0 | — | 0 | — |
| Dicuprene .. | 5 | 0 | — | 5 | 100 | 0 | — | 0 | — |

TABLE 2

OLDER CASES (MORE THAN A YEAR'S DURATION)

| Treatment | Cases | Very good | | Good | | Medium | | Failures | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % |
| Gold .. .. | 42 | 21 | 50 | 5 | 12 | 13 | 30·9 | 3 | 7·1 |
| Cupralene .. | 17 | 7 | 41·3 | 3 | 17·6 | 3 | 17·6 | 4 | 23·5 |
| Dicuprene .. | 31 | 5 | 16 | 16 | 51·6 | 4 | 12·9 | 6 | 19·4 |

than gold salts. The sooner they are used the better and quicker are the results. Copper salts are the best treatment during the subacute period when sulphonamides and antibiotics have failed to stop the advance of the disease.

2. In cases of intolerance to gold salts, copper salts can be very useful since they can be used even in the event of skin rashes, stomatitis, albuminuria, etc.

3. In cases of chryso-resistance, and in patients who no longer respond to repeated series of gold salts, their action is not so certain, but they should be tried, and sometimes, even when they are not themselves directly effective, they resensitize the patient to gold salts.

In addition to rheumatoid arthritis, copper salts have proved of value in allied conditions.

We have been satisfied with the treatment of chronic polyarticular synovitis with effusion, which seems to be a definite clinical entity. This condition, associated with a high sedimentation rate and sometimes with marked anaemia, is resistant to gold salts. In 80 per cent. of our cases the effusion has entirely or almost entirely cleared up after two or three series of injections of copper salts.

Certain cases of chronic polyarticular gout, which is often confused with rheumatoid arthritis, responded favourably to small doses of copper salts, as they do to gold salts, though the blood uric acid is not more influenced than by colchicum.

Our first attempts with ankylosing spondylitis were less successful ; but since we have raised our dosage and kept to a very strict regime in the course of injections we have had better results.

Psoriasis arthropathica, which is so closely allied to rheumatoid arthritis, generally responds to copper salts, and we shall report several cases later in which an astonishing improvement took place in both skin and joint changes.

At present we cannot exactly state the value of copper salts in infectious arthritis of known or unknown origin, or in rheumatic fever.

Whenever the sedimentation rate could be measured regularly (none of our cases was hospitalized for the full course of treatment) it was found to correspond more or less closely with the clinical improvement. Rapid fall of the figures, sometimes from 80 to 10 mm. in two or three months, was observed in early rheumatoid arthritis. These data were controlled by the Resorcin flocculation test (Vernes) and the dosage of haptoglobin (Polonowsky) whenever possible.

### Accidents

In the past ten years severe accidents with gold salts have in our own experience become very rare. This can be attributed to a proper dosage, and to careful teaching of both patient and nurse so that they will recognize the earliest symptoms of intolerance. Severe accidents can be controlled successfully with BAL and by sodium thiomalate, a compound which can also be used simultaneously

with gold salts in hypersensitive cases, to avoid reactions.

Copper salts, even with the doses mentioned above, do not as a rule cause untoward reactions. Shock may occur after an intravenous injection if the compound has not been completely dissolved. Slight transitory malaise and nausea are occasionally reported. We have observed three cases of slight jaundice, but practically no skin trouble, no albuminuria, and no thrombopenia.

## Conclusions

1. Copper salts are effective in the treatment of rheumatoid arthritis. They give better results than gold salts in the early stages of the disease.

2. In cases of longer standing they must be used if there is chryso-intolerance or chryso-resistance ; but whenever gold salts are tolerated they are to be preferred.

3. In chronic polyarticular synovitis and in psoriasis arthropathica they rank among the best treatments.

4. Their tolerance is superior to that of gold salts.

5. No copper therapy should be judged before three series have been given under the conditions described in the article.

## Les Sels de Cuivre et les Sels d'or dans la Polyarthrite Chronique Evolutive (Etude Comparative)


### Résumé

Les sels de cuivre ont montré leur afficacité dans le traitement de la polyarthrite chronique évolutive.

A la période de début, ils donnent des résultats plus rapides et plus complets que les sels d'or. Dans les cas plus anciens, ils peuvent être utilisés avec grand bénéfice en cas d'intélorance aux sels d'or. En cas de résistance à la chrysothérapie, leur efficacité est moins démontrée, dans les cas anciens. Des résultats particulièrement encourageants ont été obtenus dans deux syndromes cliniques particuliers :

1. Le rhumatisme psoriasique où le cuivre agit parfois remarquablement sur les arthropathies et même sur sur la dermatose.

2. Dans l'hydropisie polyarticulaire chronique, syndrome très spécial, où l'or s'était révélé peu actif.

La tolérance aux sels de cuivre est habituelle et aucun accident sérieux n'a été rapporté.

Avant de juger de l'efficacité des sels de cuivre, il est nécessaire d'avoir pratiqué trois séries entrecoupées d'intervalles de repos selon la posologie décrite au cours de cet article.

# SERUM ANTI-TRYPTASE IN CHRONIC RHEUMATIC DISEASE

BY

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Holmes and others (1935) reported an anti-tryptic activity of synovial fluid from cases of chronic rheumatic arthritis. The alarm reaction of Selye (1946) introduces an initial shock phase, associated with the production of adrenaline and plasmin (causing fibrinolysis: Macfarlane and Biggs, 1946), and a second phase of counter shock with a developing and increasing resistance to the repetition of the same shock-producing stimulus. The resistance evidenced as anti-plasmin is thought to be possibly identical with anti-trypsin (Biggs and others, 1947). The group of shock-producing stimuli includes severe exercise, emotional states, and trauma, which are commonly associated with the pre-rheumatic histories.

Anti-trypsin activity has been known to be a function of serum for many years (Hildebrandt, 1893). The quantitative evaluation of this anti-protease activity of the serum in relation to the activity and extent of the chronic rheumatic arthritis appeared, therefore, likely to be of value.

Trypsin is a peptidase, active at an optimum *p*H of 8·1, and otherwise it may be shown to conform to normal enzymatic behaviour and laws. While in the test-tube experiment a casein substrate has usually been employed, trypsin was, in this instance, allowed to digest as a substrate the serum proteins themselves, and the extent of the digestion was measured by estimating the substrate as precipitable proteins before and after digestion. An accurate micro-method for this estimation was both available and convenient for large numbers. A second estimation was made on each serum after extraction with ether, which either as ether or chloroform has long been known to "remove" or "destroy" the anti-tryptase effect.

## Technique

### Solutions

1. *Phosphate Buffer.*—Potassium dihydrogen phosphate, 1·3609 g., was dissolved in 9·48 ml. N/1 sodium hydroxide and distilled water added to a volume of 200 ml.

2. *Phenol.*—Phenol, 1·25 g., was dissolved in 100 ml. 0·85 per cent. sodium chloride (a strength which, on dilution, was found to be bacteriostatic and of minimal effect on tryptic digestion).

3. *Trypsin.*—Allen and Hanbury liquor trypsin co. was used.

4. *Precipitating Reagent.*—N/10 sodium orthovanadate (B.D.H.), 36 ml., was made up to a volume of 200 ml. with N/10 acetic acid.

### Methods

The method used was to shake thoroughly and vigorously 0·6 ml. of serum to be tested with an equal volume of pure ether, which was then corked and left in an upright position for at least one hour. The lower serum layer was removed with a capillary pipette and placed in an incubator (37° C.) for one hour. It was left to cool to room temperature. Two tubes of digestion mixtures were put up as follows :

| (1) | (2) |
|---|---|
| 3·6 ml. buffer | 3·6 ml. buffer |
| 0·7 ml. phenol | 0·7 ml. phenol |
| 0·4 ml. trypsin | 0·4 ml. trypsin |
| 0·3 ml. normal serum | 0·3 ml. ether-extracted serum |

These were mixed thoroughly, and 0·4 ml. taken from each ; 1·0 ml. precipitating reagent was then added to each separately. They were mixed thoroughly and left to stand at least one hour, then centrifuged for ten minutes at approximately 2,500 r.p.m., and the supernatant decanted and drained. After this the remaining precipitate was dissolved in 2·0 ml. N/100 sodium hydroxide. The concentration of protein-vanadate mixture was then measured by estimating the refractive index (although this may be done by many other methods). Both interferometer cells were filled with N/100 sodium hydroxide and the zero reading taken. The test solution was put into one cell, and the result given as the reading minus the zero reading.

The remainder of tubes 1 and 2 were put into an incubator (37° C.) for exactly twenty-four hours, then cooled to room temperature and 0·4 ml. removed from each to estimate proteins again as above.

A concentration of serum protein of 0·972 g. per 100 ml. is equivalent to 100 interferometric units. Results are expressed throughout this paper as number of interferometric units.

The difference between the protein substrate in tube 1

TABLE 1
DEFINITION OF GROUP NUMBERS

| Clinical group | Numerical group | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Normal and non-rheumatic .. | X | — | — | — | — |
| Non-articular rheumatism .. | X | X | X | — | — |
| Osteo-arthritis .. .. | — | X | X | X | — |
| Active infective arthritis.. .. | — | — | — | X | X |
| Rheumatoid arthritis .. | — | — | — | X | X |
| Endocrine-metabolic .. .. | — | — | X | X | X |
| Spondylitis ankylopoetica .. | — | X | X | X | X |
| Rheumatic fever .. .. | — | X | X | — | — |

*before and after* digestion gives the figure " A ". The difference between the protein substrate *after* digestion of tube 1 and 2 gives the figure " B ".

Two figures were thus available. In the first place, figure A, the degree of digestion of the serum proteins by a standard quantity of trypsin. Secondly, the figure B, the difference between the effective digestion of a standard quantity of trypsin upon natural serum and the same specimen after the removal of the anti-tryptic effect by ether.

## Results

Two hundred consecutive cases were examined by this technique, and in order to assess the results on a statistical basis each case had to be placed from a clinical assessment into a definite group represented by " a number ". Five group numbers were defined as in Table 1. These figures are based essentially on the extent and activity of the arthritis ; the lower-group numbers referring to more chronic and local conditions and the higher figures to generalized fulminating type of poly-arthritis.

Without detailing all the individual results, the tabulated survey of the total results (Table 2) provides the essential features from which statistical evidence may be deduced.

Assuming the practical reality of the grouping, the correlation coefficient for the " A " figures is +0·56 ; and for the " B " figures +0·62, which are respectively 7·84 and 8·75 times the standard error of the coefficient 0·07. According to the clinical grouping, arthritis as such occurs in groups 3, 4, and 5, while groups 1 and 2 are essentially non-articular. The values separating these two sections are thus for A 41 and for B 7·0. The consistency of a figure less than 41 in section A and more than 7·0 in section B with an arthritic condition can be assessed with a simple chi-square test. There were 175 cases where radiological and other proof of arthritis or the reverse was available, and after eliminating cases of spondylitis ankylopoetica and of gout :

| | Figure A | | Figure B | |
|---|---|---|---|---|
| | Below 41 | Above 41 | Above 7·0 | Below 7·0 |
| No. of cases of arthritis .. .. | 77 | 22 | 78 | 20 |
| No. of cases of non-articular rheumatism | 35 | 41 | 35 | 42 |

The Chi-square value for these tables is 16·14 and 20·5, so that the value of P is much less than 0·001 in each case. The possibility that these

TABLE 2
SURVEY OF GROUPS

| Group | No. of cases | Figure A | | | | Figure B | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean value of group | Standard deviation | Standard error of mean | Standard error between two means | Mean value of group | Standard deviation | Standard error of mean | Standard error between two means |
| 1 | 23 | **44·22** | 7·84 | 1·64 | 1·57 | **4·15** | 3·69 | 0·77 | 0·84 |
| 2 | 47 | **43·53** | 6·50 | 0·95 | 2·32 | **6·55** | 3·39 | 0·50 | 0·91 |
| 3 | 43 | **37·90** | 7·81 | 1·19 | 2·77 | **10·45** | 5·33 | 0·81 | 1·46 |
| 4 | 36 | **37·44** | 6·98 | 1·16 | 2·94 | **10·70** | 5·37 | 0·89 | 1·94 |
| 5 | 51 | **32·07** | 8·99 | 1·26 | | **16·05** | 7·63 | 1·07 | |

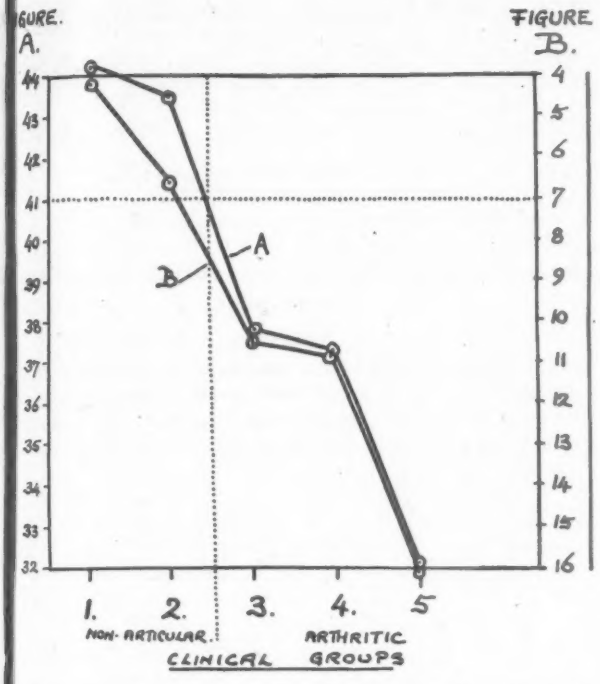


FIGURE.—The anti-tryptase function of the serum in relation to clinical groups of chronic rheumatic disease.

results occurred thus by fortuitous chance is, therefore, very small.

## Comment

These figures produce evidence that the extension and activity of rheumatic arthritis is accompanied by an increase in an anti-tryptase function of the serum. This relation is clearly demonstrated in graphical form (see Figure). The mean average figures of groups of clinical entities are treated statistically and demonstrate the significant changes in such groups of reasonable numbers. While this is an actuality, it is unreasonable to suppose that each individual case will give a figure exactly corresponding to the mean of the group. Nevertheless, the clinical use of such figures in a much greater number of cases has frequently proved useful as a diagnostic item. It is interesting to note that in respect of the anti-tryptase activity the group of spondylitis ankylopoetica generally tend to give strongly arthritic figures, while gout usually demonstrates negative or normal figures. Fluids from rheumatic bursae or joints give extremely high positive figures.

If the anti-tryptase function can be accepted, it may then be deduced that the increase in anti-tryptase in arthritic states will have an association with (*a*) an increase in an anti-tryptic substance ; (*b*) the absence of a normal tryptokinetic substance ; or (*c*) a modification in the format of the substrate.

In this latter respect the albumin-globulin ratios, which may be altered in rheumatic states, have to be considered and the fact that natural globulins are not so readily digested by trypsin (Bernheim and others, 1942). There is also the possible presence of a combined-protein complex as derived from mathematical deductions by Harkness and Whittington (1947) and akin to the " X-Protein " of Pedersen (1945) and several others. The hypothesis of a combined protein complex is derived partly from the viscometric measurement of the serum. The viscosity of the serum and plasma in chronic rheumatic disease (Cowan and Harkness, 1947) is reported as an important clinical estimation, but it has not been found to correlate at all closely with the anti-tryptic function of the serum. Finally, Ungar (1945) has produced evidence that the anti-tryptase was a function of splenic activity in that his substance (" splenin-A ") increases the rate of association between trypsin and serum anti-tryptase. Reviews of his work (*Brit. med. J.*, 1947 ; *Lancet*, 1948) and his own review (Ungar, 1947) postulates the anti-tryptase function as being due to two separate individual factors soluble in ether and aqueous solutions respectively. " The question at once arises whether splenin is the normal activator of the anti-trypsin present in the serum."

As the anti-tryptase function of the serum bears a quantitative relationship to the severity of the arthritic process, the association of this function with the physiological experiments of Ungar forms a basis to bring the question of splenic activity with that of the adrenal cortex, the pituitary, and vitamin C into closer relationship with the chronic rheumatic disorders. These have thus an association also as organic physiological reactions to emotional stimuli suggested by the work of Selye (1946) and Biggs and others (1947). The inactivation of trypsin enzymes by a low oxidation-reduction potential or the " reducing capacity " of the digest mixtures (Grob, 1946) suggests an association of these results with such substances as cysteine in the chronic rheumatic disorders and becomes allied with such therapeutic methods blocking the di-sulphydryl groups of enzymes by heavy metals (Ragan and Boots, 1947).

## Summary

1. A technique is described for a quantitative estimation of the anti-tryptase capacity of serum.

2. The results of such estimations in 200 cases of chronic rheumatic disease are tabulated and analysed.

3. A quantitative relationship between the anti-tryptase level of the serum and the extent and activity of the rheumatic arthritic condition is derived.

4. The relationship of this anti-tryptase capacity with the functional activity of the spleen, pituitary, and adrenal cortex is discussed.

My acknowledgement is due, with thanks for technical assistance, to Miss Marjorie Holt for much of the practical laboratory work.

### References

Annotation. (1947). *Brit. med. J.*, **1**, 458.
Annotation. (1948). *Lancet*, **1**, 334.
Bernheim, F., Neurath, H., and Erickson, J. O. (1942). *J. Biol. Chem.*, **144**, 259.
Biggs, R., Macfarlane, R. G., and Pilling, J. (1947). *Lancet*, **1**, 402.
Cowan, I. C., and Harkness, J. (1947). *Brit. med. J.*, **2**, 686.
Grob, D. (1946). *J. Gen. Physiol.*, **29**, 219.
Harkness, J., and Whittington, R. B. (1947). *Anal. Chim. Acta*, **1**, 153.
Hildebrandt, H. (1893). *Virchows Arch.*, **131**, 5.
Holmes, W. F., Keefer, C. S., and Myers, W. K. (1935). *J. clin. Invest.*, **14**, 124, 130.
Macfarlane, R. G., and Biggs, R. (1946). *Lancet*, 2, 862.
Pedersen, K. O. (1945). "Ultracentrifugal Studies on Serum and Serum Fractions". Uppsala.
Ragan, C., and Boots, R. H. (1947). *J. Amer. med. Ass.*, **133**, 752.
Selye, H. (1946). *J. clin. Endocrinol.*, **6**, 117.
Ungar, G. (1945). *Endocrinol.*, **37**, 329.
—— (1947). *J. Physiol. Path. gen.*, **39**, 219.

## Pouvoir Anti-tryptique du Sérum dans le Rhumatisme Chronique

### Résumé

1. L'auteur décrit une méthode de détermination quantitative du pouvoir anti-tryptique su sérum. Il présente sous forme de tableaux et analyse les résultats de ces déterminations dans deux cents cas de rhumatisme chronique. Il déduit une relation quantitative entre le taux d'anti-trypsine sérique et l'étendue et l'activité de l'arthrite rhumatismale. Il discute le rapport entre ce pouvoir anti-tryptique et l'activité fonctionnelle de la rate, de l'hypophyse et du cortex surrénal.

# THE FAMILIAL INCIDENCE OF RHEUMATOID SPONDYLITIS*

BY

BERNARD ROGOFF and R. H. FREYBERG

*From the Hospital for Special Surgery, New York City*

The familial incidence of rheumatoid spondylitis has not been adequately appreciated. The medical literature contains a few reports of families with more than one member having this form of spinal arthritis, but no serious effort to determine the familial incidence has been made. Two reports have described the existence of rheumatoid spondylitis in brothers (Stecher and Hauser, 1946 ; Weil and Allolio, 1930) ; the occurrence in identical twins has also been noted (Campbell, 1947 ; Ray, 1932). Also Scott (1942) has mentioned the development of rheumatoid spondylitis in a brother and sister, in two sisters, and in a father and son. Dawson (1935) was convinced that the familial incidence of rheumatoid spondylitis was greater than the incidence in the general population, and referred to a report by Berckhardt of a family in which the patient's mother and four brothers also had rheumatoid spondylitis. On the other hand, in the excellent and comprehensive review of 1,035 cases of rheumatoid spondylitis (the largest recorded single series) reported by Polley and Slocumb (1947), the familial incidence of the disease was not discussed.

The purpose of this paper is to report the familial incidence of rheumatoid spondylitis as it was found in a systematic study of the families of patients with rheumatoid spondylitis in the arthritis clinic of the Hospital for Special Surgery, New York City, and the Rackham Arthritis Research Unit, University of Michigan.

### Method of Study

One hundred and fourteen patients with rheumatoid spondylitis were asked whether any person among the parents, siblings, or children had pain, stiffness, or limitation of motion of the back. Thirty affirmative answers were obtained. In many instances the patients were quite positive that other members of their family had a disability similar to theirs. We were able to examine twenty-four of the suspected relatives, belonging to eighteen families. Some submitted to examination voluntarily, while others had to be sought out. Thus, no sampling bias is introduced as might have been the case had a purely voluntary group been used.

### Results

Of the twenty-four suspects investigated, thirteen cases occurring in ten families showed findings characteristic of rheumatoid spondylitis such as : back pain and tenderness, stiffness, limitation of motion of the spine, and radiographic evidence of sacro-iliac arthritis and/or calcification of spinal ligaments. Thus it was found that in ten of the 114 families one or more members of the family in addition to the presenting patient, showed evidence of rheumatoid spondylitis. If there were no other cases of rheumatoid spondylitis in the unexamined suspects, the familial incidence of this disease would be 9 per cent. (see Table). If the incidence of spondylitis in the unexamined group of thirteen families in whom there were suspects were the same as was found in the examined group, the familial incidence would increase to 13 per cent. Certainly the true familial incidence in our group of cases lies between 9 and 13 per cent. Since most of the cases were found in siblings, this high incidence becomes more remarkable when it is noted that in this group of 114 cases eight had no siblings.

### Illustrative Cases

A convincing example of the familial incidence of the disease is found in family H. (Fig. 2). H. H., the first individual to be examined, was found to have characteristic clinical and radiographic changes of advanced rheumatoid spondylitis. Not until he was specifically questioned did he state that his father and two brothers had a disability thought to be similar to his. They were subsequently examined and found to be suffering from the same disease. Radiographs of the spine in all four cases showed calcification of spinal ligaments and other ankylosing features of spondylitis (Fig. 1). It is interesting to note in the radiographs of the father (M. H.) that the sacro-iliac joints appear normal while the dorsal and lumbar spine show extensive disease of facets and ligamentous calcification.

Less striking, but showing involvement in two generations is the family F. (Fig. 3), in which a brother and a

* Read before the meeting of the American Rheumatism Association, Atlantic City, New Jersey, June 7, 1947.

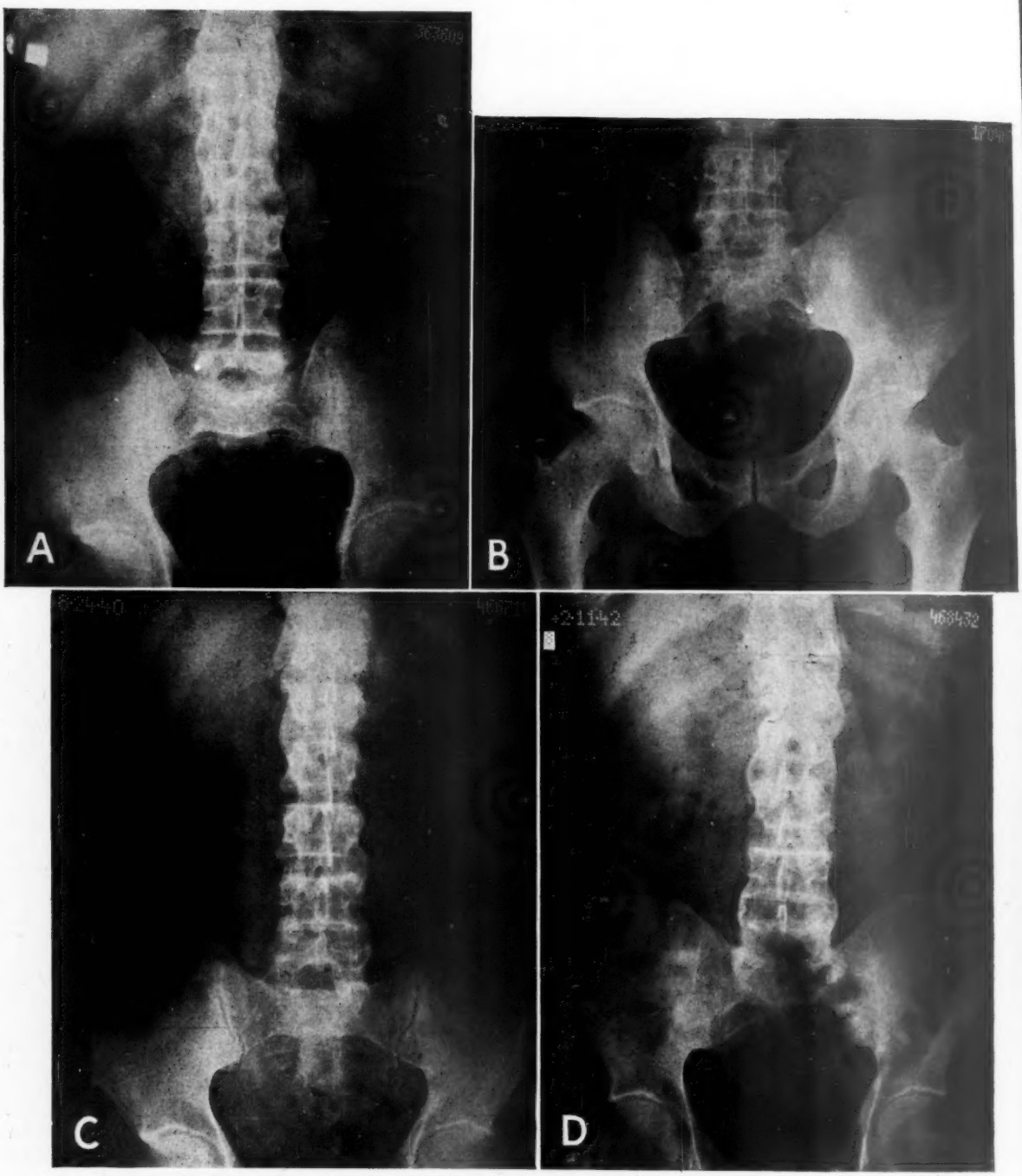


FIG. 1.—Family H. Father and three sons show evidence of rheumatoid spondylitis. Note (in C) that in the father there are extensive pathologic changes in the spinal ligament and intervertebral facets, but that the sacro-iliac joints are normal.

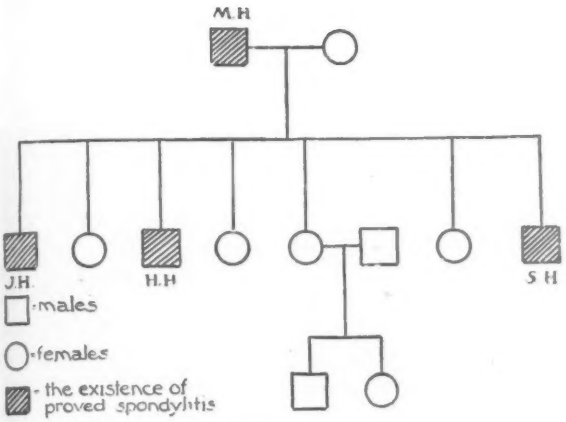


FIG. 2.—Analysis of family H.

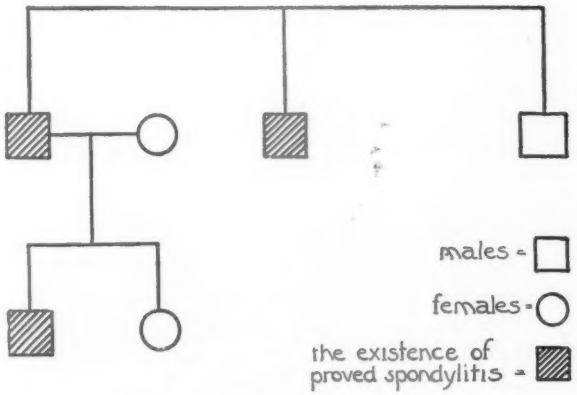


FIG. 3.—Analysis of family F.

FIG. 4.—Radiographs of the pelvis and lumbar spine of twins, aged 23, showing arthritis of the sacro-iliac joints.

son of the patient are afflicted with rheumatoid spondylitis.

Included among our cases is a pair of identical twins, aged twenty-three, each of whom while in military service began to complain of pain low in the back radiating to the buttocks. Tenderness over the sacro-iliac areas with associated lumbar muscle spasm was present. Radiographs revealed early arthritic changes in the sacro-iliac joints (Fig. 4).

## Discussion

In the post-mortem study of 10,000 vertebral columns Schmorl and Junghanns (1932) found eight cases of rheumatoid spondylitis, an incidence of only 0·08 per cent. This is in sharp contrast with the familial incidence of rheumatoid spondylitis, found in our study to be at least 9 per cent. This suggests that the familial incidence of rheumatoid spondylitis is approximately one hundred times greater than the incidence in the general population. However, it should be noted that Schmorl's study was confined to anatomical changes. It is possible that many cases of rheumatoid spondylitis diagnosed on clinical findings show such slight deviations as to be overlooked on post-mortem examination of the spine, so that the discrepancy in the incidence in Schmorl's cases, based on anatomical studies, and our cases, based on clinical studies, must be borne in mind.

The relatively high familial incidence of rheumatoid spondylitis suggests that there may be important hereditary factors. However the similarity of environmental influences within families must also be considered. Further investigations of the hereditary and environmental influences on this disease are necessary.

The practical point to be emphasized is that the managing physician should be alert to the likelihood of a higher incidence of this disease among the close relatives of his patients, and steps should be taken to discover them as soon as possible, for with early diagnosis the chance for more successful therapy is greatly increased.

## Summary

Among the close relatives of 114 cases of rheumatoid spondylitis, the familial incidence of this disease clinically was found to be at least 9 per cent.

The physician managing patients with rheumatoid spondylitis should be alert to discover other cases among relatives of these patients.

TABLE

STATISTICS OF FAMILIAL INCIDENCE RELATING TO 114 CASES OF RHEUMATOID SPONDYLITIS

| | No. | Per cent. based upon 114 families |
|---|---|---|
| Families in which spondylitis was suspected among other members from history of patient .. .. | 31 | 37 |
| Families examined .. .. | 18 | 16 |
| Families in which rheumatoid spondylitis was found by examination, among relatives .. | 10 | 9 |
| Families which could not be examined .. .. | 13 | — |

## References

Campbell, A. M. G. (1947). *Lancet*, **1**, 406.
Dawson, M. H. (1935). *Nelson's Loose Leaf Medicine*, New York, **5**, 631.
Polley, H. F., and Slocumb, C. H. (1947). *Ann. int. Med.*, **26**, 240.
Ray, M. B. (1932). *Proc. R. Soc. Med.*, **25**, 325.
Schmorl, G., and Junghanns, H. (1932). " Die gesunde und kranke Wirbelsäule in Röntgenbild ". George Thieme : Leipzig. p. 169.
Scott, S. G. (1942). " Adolescent Spondylitis ". Oxford University Press : London. p. 68.
Stecher, R. M., and Hauser, H. (1946). *Amer. J. Roentgen.*, **56**, 601.
Weil, A. J., and Allolio, B. (1930). *Dtsch. med. Wschr.*, **56**, 2038.

## La Nature Familiale de la Spondylite Ankylosante

### Résumé

On a observé parmi les proches parents de 114 malades atteints de spondylite rhumatismale l'existence de la maladie dans au moins 9 pour cent des cas. Le médecin traitant des malades atteints de spondylite rhumatismale devrait chercher à découvrir rapidement d'autres malades parmi les parents de ceux qu'il soigne.

# THE AETIOLOGY OF ANKYLOSING SPONDYLITIS

BY

H. F. WEST

*From the Department of Medicine, University of Bristol*

An attempt is here made to add to our knowledge of the aetiology of ankylosing spondylitis by marshalling what appear to be the relevant facts and by adding certain observations that have resulted from a detailed study of one hundred cases that have been under treatment or observation for from two to ten years.

### Geographical Distribution

The geographical distribution appears to be world-wide. Reports of series of cases have come from all parts of Europe and America, from Syria, South Africa, India, Australia, Japan, the Argentine, Brazil, and Chile. Seventy-four cases living within the City of Bristol have been found to be evenly distributed between the various suburbs.

### Incidence

Few attempts have been made to estimate the frequency of the disease in the general population. Clausen and Kober (1936) accepted an incidence of 1 in 1,000, based on the autopsy findings of Schmorl and Junghanns (1932), who found six or eight definite cases among 10,000 bodies coming to necropsy at the city hospital of Dresden. More than half the spines were only examined *in situ* by palpation. Other figures relate to highly selected material. Bachmann (1930) found sixty-six examples among 3,201 spines he had studied radiographically. Willis (1933) found smooth ankylosis of the sacro-iliac joints in 1·2 per cent. of 1,509 museum skeletons. Boland and Shebesta (1946) found 18 per cent. affected among 6,000 consecutive admissions to an American Army Rheumatism Centre. The ratio of cases of "rheumatoid spondylitis" to "peripheral rheumatoid arthritis" among U.S. Army patients was reported as 1 to 3 (Boland and Present, 1945). The ratio in civilian practice has been estimated by various workers as 1 : 11, 1 : 13, and 1 : 19 (Hare, 1940; Dunham and Kautz, 1941; Tyson, 1937), but the figures are of little value when an attempt is made to estimate the incidence of ankylosing spondylitis, owing to the selected nature of clinic material, the general misdiagnosis of mild cases in general practice, and the variable criteria of diagnosis adopted for both diseases.

In Bristol the orthopaedic work is centralized and there is reason to believe that almost all the cases diagnosed during the last five years have passed through the spondylitis clinic at the *x*-ray therapy department of the Royal Hospital. As only some 2 per cent. of the patients have been found to manifest the disease for the first time after the age of forty, it is possible to obtain a rough estimate of the number of cases in Bristol from a simple histogram (see Figure). An average age at death of 60 years is assumed.

The total of cases from the City, both known cases and those assumed missed, is 144. If one further assumes that 70 per cent. of the population of 420,000 are, or have been, "at risk", one arrives at an incidence of 1 in 2,000 of the general population "at risk". This figure will be used below when the expected incidence of multiple cases within sibships is estimated.

After each world war it was suggested that the incidence had increased. The segregation at those times of young adult males with "rheumatic" complaints is the likely explanation of this clinical impression. Such explanation was accepted by Schmorl and Junghanns after the first war. That the

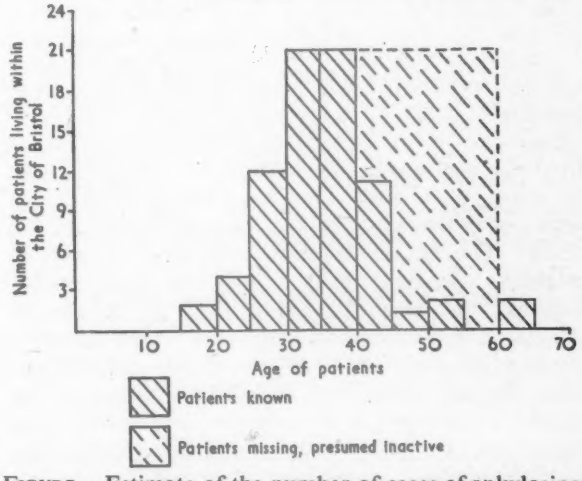


FIGURE.—Estimate of the number of cases of ankylosing spondylitis in Bristol.

disease is not of recent origin is shown by numerous descriptions dating back to 1700, by a suggestive clinical description from the Beloved Physician (Luke xiii, verse 11), and by the study of skeletons of Nubians who lived many thousands of years before Christ.

### Sex Distribution

Forestier (1940) thought the disease was rare in women, but Scott (1942) found 30 per cent. of women among his cases. The sex incidence reported in most large series of patients has been approximately ten males to one female. At the Mayo Clinic the figures were 931 men to 104 women (Polley and Slocumb, 1947). Of 134 patients seen here during the last ten years twelve were women, a ratio of 1 to 10.

### Type and Occupation of Person Affected

The type of individual affected has been the subject of much comment. Two statements of Scott (1942) warrant attention. He found that 90 per cent. of three hundred were swimmers and divers, mostly well above the average. At Bristol forty-five of one hundred were found to be swimmers, not a high percentage for the district; and fifty-three had indulged in organized field games after leaving school. At least it may be said that the disease is found more among the active than the weaklings. Scott's other statement was that many had a characteristic facies, "ferret face". Profile photographs were taken of a series of patients, but the practice was discontinued when it was realized that there was no common feature.

No occupational predilection has been noted. Of one hundred patients only thirty-three had been engaged in heavy manual labour. There is no evidence to suggest that economic factors are concerned.

### Age and Mode of Onset

The onset occurs when growth has ceased, or is ceasing, in bone, when the secondary epiphyses have appeared, or are appearing, and when articular cartilage is showing chemical change by beginning to stain blue with haematoxylin. It does not begin or flourish during the physical decline of the body. The course is usually said to be one of relentless progress with remissions and exacerbations, but when case histories are examined it is found that in most there have been three phases: the first being of isolated attacks of pain and stiffness occurring at increasingly frequent intervals; the second a florid phase of continuous symptoms and constitutional upset; and the third of declining activity and minor relapses. In severe cases the florid phase is prolonged, while in mild cases it may never be reached. This pattern of progress with the constant symmetrical anatomical sequence of involved structures, occurring as it does at a particular period in life, suggests a local defect in metabolism rather than an infection.

This picture of the disease coupled with the predominance of affected males and the work of Batson (1940) on the spread of prostatic carcinoma has suggested to Buckley (1945) the possibility that a "morbific agent" arising in the prostate may be the cause. The occurrence in some severe cases of prespondylitic lesions in the joints of the lower limbs, as well as the evidence to be presented below, detracts from this otherwise attractive theory.

### The Connective-Tissue Ground Substance

Of the symptoms attention is directed to the characteristic stiffness. This stiffness develops during rest and can be "worked off", and though not peculiar to ankylosing spondylitis is a striking, persistent, and invariable symptom. Muscle spasm occurs commonly when the back symptoms are acute, but is quite different in nature from the stiffness. There is no evidence that it is due to abnormal tone and, so far, pathologists have been unable to detect any abnormality in biopsy material from affected muscles (Desmarais and others, 1948). Any theory as to the aetiology of the disease must account for this stiffness as well as for the lesions in the spinal joints. As yet little attention has been paid to the connective-tissue ground substance. Hyaluronic acid would appear to be the lubricant of the tissues as well as of the joints, which latter are, embryologically, but clefts within connective tissue. An undue increase in the viscosity of the connective tissue lubricant might well occasion stiffness. There is evidence to suggest that the viscosity of this connective tissue ground substance is normally increased by rest (Duran-Reynals, 1942) and that age, sex, and heredity are factors in connective-tissue permeability in animals. The viscosity of the connective-tissue ground substance is not, of course, the only factor governing permeability. The secretion of synovial fluid is increased by exercise and decreased by rest, and an analogous situation may well obtain in the connective tissue. It is suggested that a defect in the metabolism of hyaluronic acid or related substances may play a part in the aetiology of the disease. It would be interesting to know what effect an intravenous infusion of homologous hyaluronidase has upon the stiffness. Salicylates appear to relieve the stiffness temporarily, though by what mechanism is not known. Unconfirmed work of Gil and Guerra (1947) suggests that salicylates interfere with the spreading effect

of testicular hyaluronidase in human skin. Quinn (1948) has reported increased anti-hyaluronidase activity in the serum of patients with " active acute rheumatic fever ", and Glick and Gollan (1948) have reported an increase of inhibitor to hyaluronidase in the serum of patients with poliomyelitis. Whether a specific anti-hyaluronidase was concerned, or whether there was simply an increase in the non-specific hyaluronidase inhibitor of the serum, was not known. One wonders whether this has any bearing on the fact that many patients with quiescent ankylosing spondylitis experience a fresh access of stiffness with a febrile illness such as influenza.

**Iritis.**—The association of " diffuse " iritis is of great interest ; it is not commonly associated with any other disease. Of one hundred patients, no less than fifteen had had iritis at least once, whereas Sorsby and Gormaz (1946) found only one patient with evidence of past iritis among 316 " non-rheumatic " hospital patients. This comparison is not quite true, since Sorsby and Gormaz recorded only objective evidence and did not accept " histories ". The iritis of ankylosing spondylitis often recovers without leaving any objective evidence. Schley (1937), studying diffuse iritis, found that of seventy-three patients fifteen had ankylosing spondylitis. The particular interest lies in the fact that the ciliary body contains hyaluronic acid and the aqueous and vitreous humours contain both hyaluronic acid and hyaluronidase (Meyer. 1947). Blair in 1942 drew attention to the chemical relation between cartilage and the ciliary body.

### Effect of Pregnancy

Pregnancy made little difference to one patient, but to another it occasioned considerable relief and an absence of back stiffness (objective) lasting for two weeks into the puerperium in two pregnancies.

## Laboratory Investigations

Laboratory investigations have so far failed to reveal any abnormality in the inorganic constituents of the blood (Hemphill and Reeves, 1945 ; and others). Spectrographic analysis of incinerated whole blood for trace elements at first suggested an excess of copper, but subsequent examination of some twenty further samples from active cases and controls failed to show any constant abnormality. (This work was kindly undertaken for the author by Dr. M. N. Thruston of I.C.I. Ltd.) There is no evidence that fluorine is concerned. The vertebral ankylosis that is seen occasionally among patients suffering from severe fluorosis, with or without renal disease, is quite unlike that seen in ankylosing spondylitis. Blood lipids and blood phosphatases have also been found to be present in normal quantities (Hemphill and Reeves, 1945), though a significant rise in alkaline phosphatase has been reported by Buckley (1945). No distinctive pattern of plasma proteins has been noted. It has been said that the increased erythrocyte sedimentation rate points to an infective aetiology, but a number of non-infective conditions, such as gout and closed injuries, occasion a similar rise. In the cerebrospinal fluid the only abnormality noted has been an increase in protein (Ludwig and others, 1943), most marked—up to 98 mg. per 100 ml.—in patients with active disease (Boland and others, 1947). It is suggested that this is due to hyperaemia of the spinal meninges secondary to the intense activity in the adjacent joints and vertebral bone. The excretion of 17-ketosteroids has been found to be well above the normal range (Davison and others, 1947). This work awaits confirmation. Steffens (1938) and others have postulated an underlying endocrine disturbance, and Ködderman (1939) treated his patients for an alleged hypofunction of the testes and pituitary, but the administration of androgenic and oestrogenic preparations by various workers has not resulted in any marked benefit.

No organisms have been isolated from affected joints. Gonorrhoea has been regarded by many as a factor in the aetiology. Sir Jonathan Hutchinson suggested that gonorrhoea was the cause of the case that Davies-Colley described so clearly in 1885. Recent studies in America have shown that a history of gonorrhoea is no more common among patients with ankylosing spondylitis than it is among the general army population. Scott (1942) tried to incriminate the tubercle bacillus. He found evidence of calcified mesenteric glands in 95 per cent. of four hundred radiographs. This finding has not been confirmed by others. The radiographs of a hundred patients seen here revealed only sixteen examples. Goldfain (1943) found raised agglutination titres against Brucella organisms in a considerable percentage of his patients, but the results were not controlled and the endemicity of Brucellosis was not known. A local spondylitis that heals by ankylosis is not rare in Brucella infections, but it does not resemble the disease under discussion. No other abnormal agglutinins have been reported, and Perry (1940) did not find in the serum any abnormal resistance to fibrinolysis.

## Pathological and Radiographic Studies

Pathological and *x*-ray studies reveal the following pertinent facts :

1. The joints affected are those that are most liable to continuous strain and movement, namely the sacro-iliac joints, the vertebral apophyseal joints and the rib articulations, and the disease progresses from the joints bearing the greatest

strain to those bearing less. It may be noted that these joints, perhaps more than any others, have had to adjust themselves recently in evolution to an alteration in the direction of the strain. (Fox (1939) attempted to relate arthritis to joint size and body weight.)

2. The calcification of the vertebral ligaments occurs where the strain upon the bone at their attachments is greatest. This calcification provides reinforcement at defective ligament-bone junctions ; it is not a physiological response to faulty alignment. Spinal curvature from other causes, even when the vertebrae are markedly osteoporosed, does not call forth this response, except in the local ankylosis that may occur between two diseased vertebrae (as in tuberculosis, typhoid fever, and undulant fever).

Calcification in the ligamentous attachments about the pelvis, seen best between the alae of the sacrum and the ilium and at the attachment of the hamstring muscles to the tuber-ischii, is also proportional to the strain imposed. This was well shown in a severely affected patient who had had an amputation through one thigh in childhood. Buckley (1945) postulated a defect in the metabolism of bone alkaline phosphatase giving rise to a mobilization of calcium from the bone and its immediate deposition in the adjacent ligaments. From a study of many serial radiographs it is clear that the ligamentous calcification is often long delayed in the presence of marked osteoporosis of the vertebrae. The joint pathology so far described resembles microscopically that found in rheumatoid arthritis, but muscle biopsies have failed to reveal the extra-articular pathology of that disease (Desmarais and others, 1948). Güntz (1933), who made one of the first thorough histological studies of the joint lesions, could find no abnormality in the vertebral bodies.

### Effects of Treatment

The effect of treatment has not thrown any light on the nature of the disease, though Blair (1942) has speculated in this connexion on the disappearance of mast cells from the vicinity of tumours following irradiation. (Mast cells produce heparin —mucoitin polysulphuric acid—a substance chemically related to chondroitin sulphuric acid and hyaluronic acid.) Deep *x*-ray therapy, especially "intensive" treatment, does relieve severe pain and facilitate orthopaedic measures, but how it brings this about is not known. Whether *x*-ray therapy affects the course of the disease is as yet uncertain, for most reports of treatment have been couched in very similar terms for the last twenty years (Woldenberg, 1924 ; Stockman, 1926 ; Krebs and Vontz, 1934 ; Swaim, 1939 ; Forestier, 1939 ; Smyth and others, 1941 ; Hilton, 1943 ; Wyatt, 1945 ; McWhirter, 1945 ; Williams, 1948).

### Hereditary Factors

Though many reports have been made of families with more than one affected member (for example that of Campbell, 1947), statements to the effect that inheritance plays no part in the aetiology of the disease are still to be found in the most recent textbooks. In 1938 Clausen and Kober published a paper on the inheritance of "Becheterew's" disease. They pointed out the fact so often forgotten that "history taking" does not reveal nearly so much as a thorough investigation of the family. They investigated the families of ten cases from among eighty-one ; the others, they said, were too difficult to get hold of. In these ten families they found nine secondary cases, four alive and five dead (three with medical evidence and two without). They found one secondary case in each of three families, two in one family, and four in one family. Although they mentioned no criteria for diagnosis, their evidence was certainly impressive. Rogoff and Freyberg (1948) studied 114 patients and found thirty-four with family histories of disabilities of the back. Of these thirty-four they investigated eighteen and found ten families with multiple cases. They estimated a family incidence of 9 to 13 per cent. Of the hundred patients studied in this series there were ten who knew so little of their families that the recording of their histories was worthless. The remaining ninety patients came from eighty-three families. In these there were ten secondary cases among brothers and sisters. Eight families contained two affected members, and one three. The incidence of multiple cases within sibships was thus nine in eighty-three, or approximately 11 per cent., which is more than a hundred times greater than would be expected assuming a random distribution.

Taking the incidence among those at risk as 1 in 2,000 and the fact that the average number of individuals per affected sibship was 4·45, and assuming a random (Poisson) distribution, one may estimate the expected incidence of multiple cases within sibships as follows :*

| No. of patients per family .. .. | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| No. of families found | 41,907 | 74 | 8 | 1 |
| No. of families expected | 41,907 | 74 | 0·065 | 0·00003 |

* I am indebted for the series to Dr. Munson, Physicist at the Bristol Royal Hospital.

These figures are likely to under-estimate the incidence of multiple cases within sibships, since a number of sibs with suggestive symptoms have so far remained inaccessible. The existence of the disease in other than siblings has not been recorded, since the material so far collected is as yet too incomplete.

Speculation as to the reason for the uneven sex incidence led to the question, "Why do nine out of every ten women, who presumably inherit the abnormal genetic material, fail to manifest the disease?" This in turn led to a further study of the families of those women who *had* manifested the disease, and it was found that of the ten women who had brothers no less than four had an affected brother.

The acceptance of these findings depends upon the acceptance of the fact that bilateral sacro-iliitis is "ankylosing spondylitis". It is here assumed that this is the case for three reasons. First, because most cases of bilateral sacro-iliitis do subsequently develop radiological evidence of involvement of the lumbar spine. Of forty-five patients who, when first seen, had only sacro-iliac involvement, thirty-two have already progressed to lumbar spine involvement. Secondly, because it is not possible to differentiate between those cases which will progress to spinal involvement and those which will not. Thirdly, because cases showing radiological evidence of sacro-iliitis alone may be found among the brothers and sisters of the severely affected (? forme fruste). The requirements for diagnosis were, in addition to a typical history of signs and symptoms, radiological evidence of bilateral sacro-iliitis which in its minimal form had to show at least multiple circumscribed areas of sclerosis or relative osteoporosis in the lower part of the joint. It has been said that the earliest radiological signs were "lack of definition", "ground-glass appearance", and "haziness". An *x*-ray study of the sacro-iliac joints of forty normal University students showed that such appearances could not be accepted as criteria of sacro-iliac involvement.

The facts reviewed are consistent with the finding that heredity plays a major role in the aetiology of the disease. Further study of the relatives of patients, other than siblings, is required to establish the type of inheritance involved. This study might well be coupled with a search for cases of rheumatic fever among both patients and relatives, since many workers suspect some relationship between acute rheumatism and ankylosing spondylitis (Polley, 1948). Several patients in this series had attacks of polyarthritis intermediate between acute rheumatic fever and rheumatoid arthritis, either before or at the onset of their spinal symptoms. Twelve gave a history of having had acute rheumatic fever, and five actually had mitral stenosis.

The mechanism of expression of the defective genetic material must now be sought. It is suggested that a histochemical study of biopsy material from normal and acutely affected structures may provide a first step.

### Summary and Conclusions

1. The facts concerning the disease which might be expected to have a bearing on its aetiology are reviewed and some of the theories so far propounded are discussed.

2. Observations on the nature of the disease process and of the affected joints are made, and emphasis is laid on the chemical relationship that exists between the affected structures (connective-tissue ground substance, synovial fluid, the chemical constituents of the eye, cartilage, and ligament).

3. The incidence of the disease in the general population is discussed, and evidence is produced which suggests that the inherited factor is sex influenced.

4. It is concluded that the facts so far known point to a local metabolic defect in articular structures subject to continuous stress and in bone-ligament attachments similarly subject, with heredity as a major aetiological factor.

For clinical facilities and for encouragement and advice I am greatly indebted to Prof. C. Bruce Perry.

#### References

Bachmann, A. (1930). *Fortschr. Geb. Roentgen.*, **42**, 500.
Batson, O. V. (1940). *Ann. Surg.*, **112**, 138.
Blair, H. C. (1942). *Surg. Gynec. Obstet.*, **74**, 663.
Boland, E. W., Headley, N. E., and Hench, P. S. (1947). *Annals of the Rheumatic Diseases*, **6**, 99.
——, and Present, A. J. (1945). *J. Amer. med. Ass.*, **129**, 844.
——, and Shebesta, E. M. (1946). *Radiology*, **47**, 551.
Buckley, C. W. (1945). *Annals of the Rheumatic Diseases*, **4**, 54.
Campbell, A. M. G. (1947). *Lancet*, **1**, 406.
Clausen, F., and Kober, E. (1936). *Z. Konstit-lehr.*, **22**, 268.
Davies-Colley, N. (1885). *Trans. Path. Soc.*, **36**, 359.
Davison, R. A., Koets, P., and Kuzell, W. C. (1947). *J. clin. Endocrinol.*, 7, 201.
Desmarais, M. H. L., Gibson, H. J., and Kersley, G. D. (1948). *Annals of the Rheumatic Diseases*, **7**, 139.
Duran-Reynals, F. (1942). *Bact. Rev.*, **6**, 197.
Dunham, C. L., and Kautz, F. G. (1941). *Amer. J. med. Sci.*, **201**, 232.
Forestier, J. (1939). *Radiology*, **33**, 389.
Fox, H. (1939). *Trans. Amer. phil. Soc.*, vol. **31**.
Gil, J. R., and Guerra, A. F. (1947). *Arch. Inst. Cardiol. Mex.*, **17**, 733.

Glick, D., and Gollan, F. (1948). *J. infect. Dis.*, **83**, 200.
Goldfain, E. (1943). *J. Lab. clin. Med.*, **28**, 1226.
Güntz, E. (1933). *Fortschr. Geb. Roentgen.*, **47**, 683.
Hare, H. F. (1940). *New Engl. J. Med.*, **223**, 702.
Hemphill, J. E., and Reeves, R. J. (1945). *Amer. J. Roentgen.*, **54**, 282.
Hilton, G. (1943). *Proc. R. Soc. Med.*, **36**, 608.
Kõdderman, O. (1939). *Munch. med. Wschr.*, **86**, 731.
Krebs, W., and Vontz, O. (1934). *Dtsch. med. Wschr.*, **60**, 100.
Ludwig, A. O., Short, C. L., and Bauer, W. (1943). *New Engl. J. Med.*, **228**, 306.
McWhirter, R. (1945). *Brit. J. Radiol.*, n.s. **18**, 302.
Meyer, K. (1947). *Physiol. Rev.*, **27**, 335.
Perry, C. Bruce (1940). *Annals of the Rheumatic Diseases*, **2**, 147.
Polley, H. F. (1948). Personal communication. Mayo Clinic.
——, and Slocumb, C. H. (1947). *Ann. int. Med.*, **26**, 240.
Quinn, R. W. (1948). *J. clin. Invest.*, **27**, 471.
Rogoff, B., and Freyberg, R. H. (1948). *Annals of the Rheumatic Diseases*, **7**, 40.
Schley, H. (1937). *Klin. Mbl. Augenheilk.*, **98**, 780.
Schmorl, G., and Junghanns, H. (1932). "Die Gesunde und Kranke Wirbelsaule". Leipzig.
Scott, S. Gilbert (1942). "Adolescent Spondylitis". Oxford University Press. London.
Smyth, C. J., Freyberg, R. H., and Lampe, I. (1941). *J. Amer. med. Ass.*, **117**, 826.
Sorsby, A., and Gormaz, A. (1946). *Brit. med. J.*, **1**, 597.
Steffens, W. (1938). *Dtsch. med. Wschr.*, **64**, 1438.
Stockman, R. (1926). *Edinb. med. J.*, **33**, 597.
Swaim, Loring T. (1939). *J. Bone Jt. Surg.*, **21**, 983.
Tyson, T. L. (1937). *Med. Clin. N. Amer.*, **21**, 1755.
Williams, D. I. G. (1948). *Annals of the Rheumatic Diseases*, **7**, 21.
Willis, T. A. (1933). *Surg. Gynec. Obstet.*, **57**, 147.
Woldenberg, S. C. (1924). *J. Amer. med. Ass.*, **82**, 1027.
Wyatt, H. (1945). *Brit. J. Radiol.*, n.s. **18**, 301.

## L'Etiologie de la Spondylite Ankylosante

### Résumé et Conclusions

L'auteur passe en revue les faits concernant la spondylite ankylosante susceptibles d'avoir une importance au point de vue étiologique et discusse quelques-unes des théories proposées jusqu'ici. Il relate ses observations sur la nature du processus pathologique et des articulations atteintes, et insiste sur la parenté chimique existant entre les tissus affectés (substance fondamentale du tissu conjonctif, liquide synovial, les constituants chimiques de l'oeil, cartilage, et ligaments). Il discute la fréquence de la maladie dans la population en général, et donne des preuves qui suggèrent que la facteur héréditaire est lié avec la sexe. Il conclut que les faits connus jusqu'à présent indiquent l'existence d'un trouble local du métabolisme des structures articulaires et des insertions ligamentaires soumises à un effort continu, l'hérédité constituant un facteur étiologique important.

# OPAQUE ARTHROGRAPHY OF THE KNEE JOINT

BY

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There are occasions when radio arthrography of the knee joint is of value, both as an aid to diagnosis in obscure cases and for assessing the results of treatment. Cullen and Chance (1943) and Somerville (1946) have shown the value of air arthrography in cases of lesions of the menisci, and before that Lagergren (1934) used a radio-opaque medium for the same purpose; but it is felt that opaque arthrography should have a wider application than this as it will give useful information, sometimes of a more precise nature than can be obtained in any other way, as to the state of the articular cartilages, the synovial membrane, the presence of non-opaque bodies within the joint, or the relationship of an opaque body to the synovial cavity. Opaque arthrography has been used in other joints, notably in the hip joint by Sievers (1926-7), Leveuf and Bertrand (1937), and Severin (1939), in cases of congenital dislocation.

The first arthrogram in this series was taken at the Princess Elizabeth Hospital, Exeter, in March 1946, and since that time a further forty-seven knees (forty-four patients) have been examined in this way at the Princess Elizabeth Orthopaedic Hospital, Exeter, Mount Gold Hospital, Plymouth, and Musgrove Park Hospital, Taunton. A preliminary report on sixteen cases was made at the British Orthopaedic Association Spring Meeting at Exeter in May 1947.

## Opaque Media

The opaque media used have been two proprietary preparations of 3, 5, di iodo-4-pyridone-N-acetic acid-diethanolamine, commonly known as "Diodone" and originally used for excretion urography. The preparations used are "Pylumbrin" (Boots) and Diodrast (Winthrop), which consist of a 35 per cent. solution of the drug in water, giving a neutral and stable solution which can be sterilized by heat. The solution is much heavier than synovial fluid and the two do not readily mix without shaking. A 17·5 per cent. solution has been used in some cases, but, owing to its rapid absorption the time during which satisfactory radiographs can be obtained is short.

**Dosage.**—The dosage is limited rather by the capacity of the knee joint than by the toxicity of the opaque medium. Normally up to 30 c.cm. may be given intravenously to an adult, whereas it has not been found necessary to inject more than 12 c.cm. into a knee joint, 9 c.cm. being usual for an adult. In children the dosage is proportionately reduced. In one patient (Fig. 16), the knee joint did not communicate with the suprapatellar pouch; this was not known at the time of injection and 9 c.cm. of medium were injected. This seemed to have been rather too much for a joint thus reduced in capacity, for the knee was rather tense for three days afterwards, but it recovered completely in a few days.

**After-Effects.**—The injection is often followed by a small effusion with little or no pain; this subsides in a few days: in no case has there been any ill-effect lasting beyond a week. Occasionally a joint which formerly contained an effusion has been clinically and, in the patient's opinion, better than before arthrography. Lagergren (1934), using "Perabrodil" (Bayer), which is also a 35 per cent. solution of "Diodone", carried out biopsies of synovial membrane in those cases subsequently submitted to arthrotomy. In no case was there histological evidence of irritation. This has been confirmed in two of the present cases.

"Diodone" is said occasionally to give rise to allergic phenomena, when given intravenously. No such phenomena have been seen in this series, but in allergic subjects, and particularly in those with an iodine sensitivity, the examination should be approached with caution.

## Method of Administration

The method of administration has been as follows: After thorough skin preparation and local infiltration with 2 per cent. procaine solution, a needle of moderate bore is made to enter the knee joint: any excess of synovial fluid is aspirated from the joint and about 5 c.cm. of this is thoroughly mixed with the medium which is then injected into the joint. The needle is withdrawn and the puncture covered with a sterile dressing, which is loosely bandaged. The knee joint is then made to move through its full range a few times and the patient is taken to the *x*-ray department. The mixture of the drug with synovial fluid seems to help the diffusion of the medium throughout the joint, though there has been no delay of this in "dry" joints where such mixing has not been possible.

For two days afterwards, the patient is kept in bed, carrying out non-weight-bearing exercises.

## Radiographic Technique

No specialized radiographic technique has been used. Antero-posterior lateral, and antero-posterior oblique

views (with the limb medially and laterally rotated to forty-five degrees) are taken as a routine. A tangential view of the patello-femoral joint is taken, where indicated, as are also postero-anterior oblique views.

The drug is absorbed fairly rapidly, but good shadows are usually obtainable for fifteen minutes after injection. In the three cases tested the shadow due to the drug became indistinguishable between three and a half and four hours afterwards.

### Results

The normal antero-posterior view shows the suprapatellar pouch of normal size and shape; a thin and regular film of medium extends across the middle of the joint, outlining the cartilaginous covering of the bony surfaces: towards either side of the joint this film, which represents the true joint space, splits to enclose the menisci, which are triangular in section. The lateral meniscus is often bounded by a vertical shadow, which usually dips below the upper surface of the tibia: this is the synovial sheath of the popliteus. These characteristics are seen in Fig. 1, but the suprapatellar pouch is smaller than usual as a result of an old wound. A normal medial meniscus is also well seen in Fig. 8.

The normal lateral view (Fig. 2) shows the suprapatellar pouch of normal size and shape, the outline of the cartilaginous surface of the patella, and a film of medium covering the articular cartilage of the femur, which meets that covering the tibial joint surface and so outlines the infrapatellar pad of fat. The film of medium extends between the contiguous surfaces of the femur and tibia and splits again to extend over the back of the femoral and tibial condyles. Sometimes this posterior pouch of the joint is more bulky.

The oblique views are used mainly to demonstrate the menisci. The external oblique, taken in an antero-posterior direction, with the limb rotated outwards forty-five degrees (Fig. 3), shows the anterior end of the lateral meniscus and the posterior end of the medial meniscus. Both are triangular in section, with smooth surfaces. The internal oblique view (Fig. 4) shows the anterior end of the medial meniscus and the posterior end of the lateral meniscus: both are of normal appearance, the latter being bounded peripherally by a vertical film of medium, which is occupying the synovial sheath of the popliteus tendon.

Fig. 5, a tangential view of the patello-femoral joint, shows a smooth regular film of medium between articular cartilages of equal depth except at the medial end, where there is some irregularity, probably due to early arthritic change: the film of medium is denser than usual.

Figs. 6 and 7 are arthrograms of the knee of a boy of nearly seven years. The arthrograms show well the depth of cartilage which clothes the epiphyses of the femur and tibia and the patella at this age; the defining of the cartilage gives a much more adult outline to the bone-ends. The medial meniscus is well seen, but the lateral meniscus is less definite in outline.

Fig. 8 shows a tear of the lateral meniscus, represented by a band of the medium traversing the shadow of the lateral meniscus, which contrasts well with the normal shadow of the medial meniscus. Unfortunately, it has not yet been possible to confirm this finding by operation, as the patient had a severe hysterical palsy of his hand which, it was considered, should have priority of treatment over his knee condition, which was causing him relatively slight disability.

Fig. 9 shows an oblique view of a medially rotated knee; the normal triangular outline of the posterior end of the lateral meniscus is just visible; the shadow of the anterior end of the medial meniscus is shortened and rounded. This finding was confirmed at operation, which revealed a "bucket-handle" tear of the medial meniscus, with displacement into the middle of the joint.

Figs. 10 to 13 illustrate a case of villous arthritis. Figs. 10 and 11 are of pre-operative films, showing a grossly enlarged suprapatellar pouch with much folding of the synovial membrane; some air which had inadvertently been allowed to get into the joint is seen in the posterior pouch. The upper part of the suprapatellar pouch had hardly been penetrated by the medium and was found at operation to have been almost completely separated from the joint by a synovial septum. Figs. 12 and 13 are of the films taken eleven months after synovectomy: the suprapatellar pouch is of normal size, though it still shows a tendency to folding of the synovial membrane. The lower part of the joint is seen to be normal and there is a good posterior pouch.

Fig. 14 illustrates a case of chronic fibrinous arthritis of the knee occurring late in the course of chronic infective polyarthritis. The arthrograms show several films of opaque medium between translucent areas in the suprapatellar pouch, the nature of which was not fully appreciated until synovectomy was carried out: the suprapatellar pouch was then found to contain several large masses of fibrinous material, which constituted the "filling defects" noted radiographically.

Figs. 15 and 16 are taken from a case of an old injury to the knee joint, which included a depressed fracture of the lateral tibial condyle and lesions of both menisci and both cruciate ligaments. Fig. 15

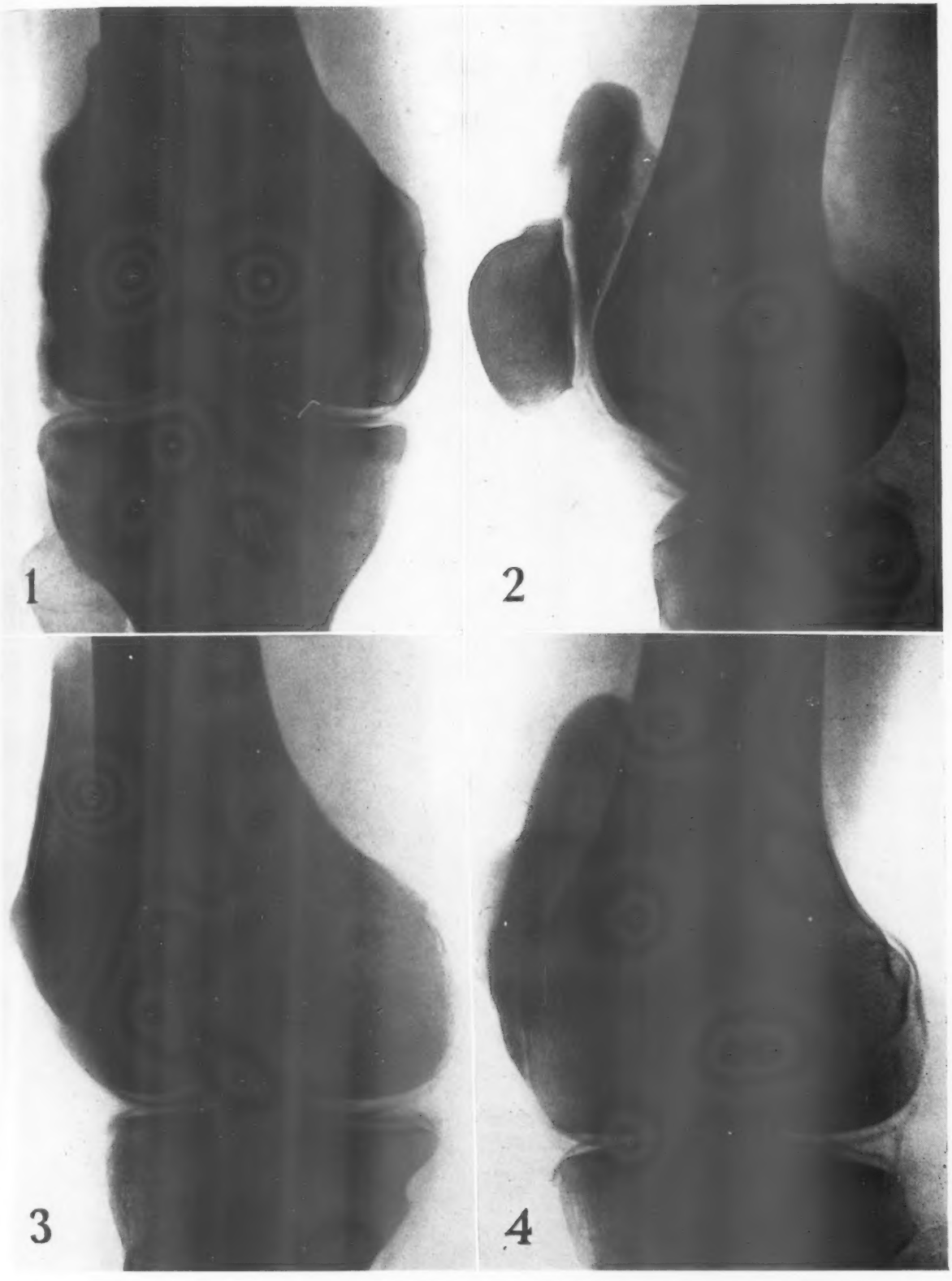



FIG. 1.—Normal arthrogram, antero-posterior view.

FIG. 2.—Normal arthrogram, lateral view.

FIG. 3.—Normal arthrogram, antero-posterior oblique, in external rotation.

FIG. 4.—Normal arthrogram, antero-posterior oblique, in internal rotation.

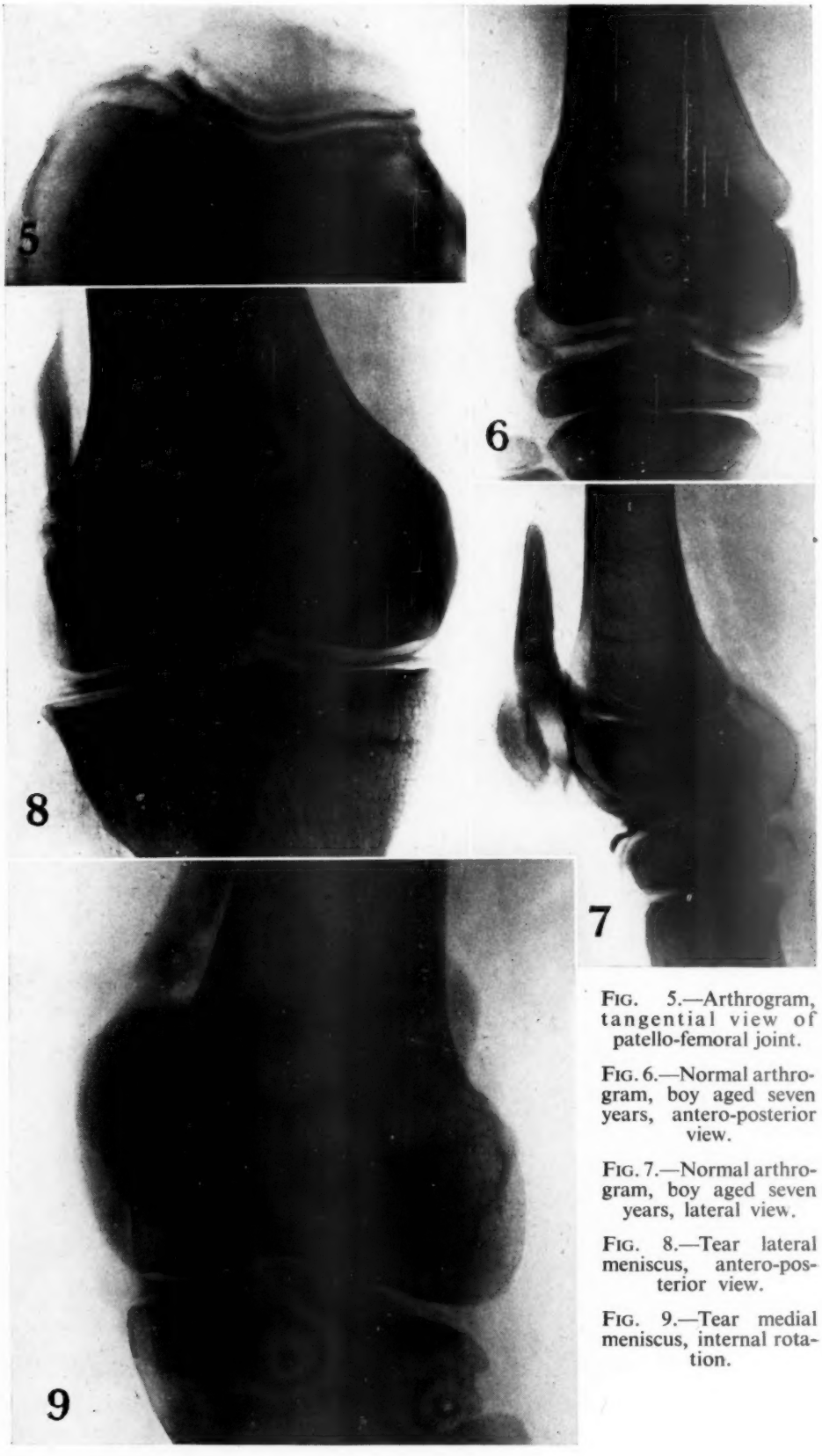


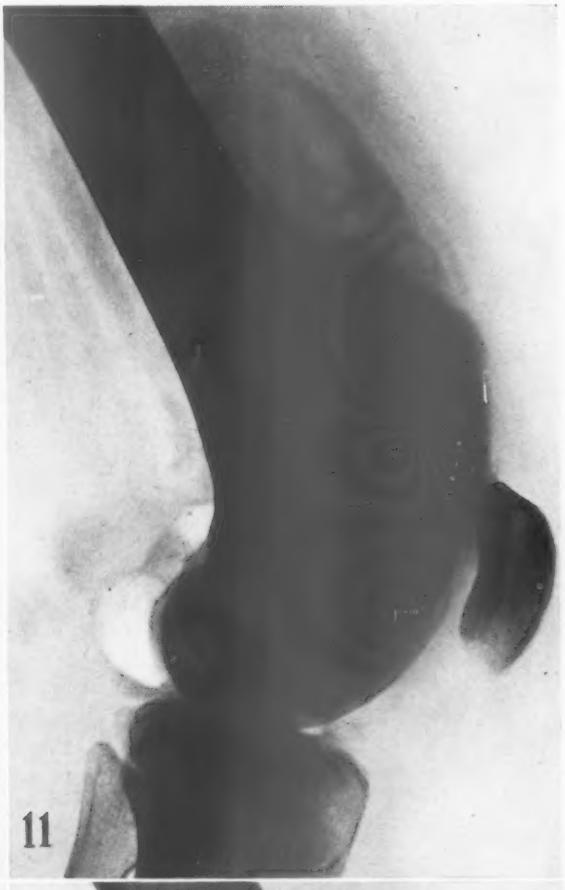

FIG. 5.—Arthrogram, tangential view of patello-femoral joint.

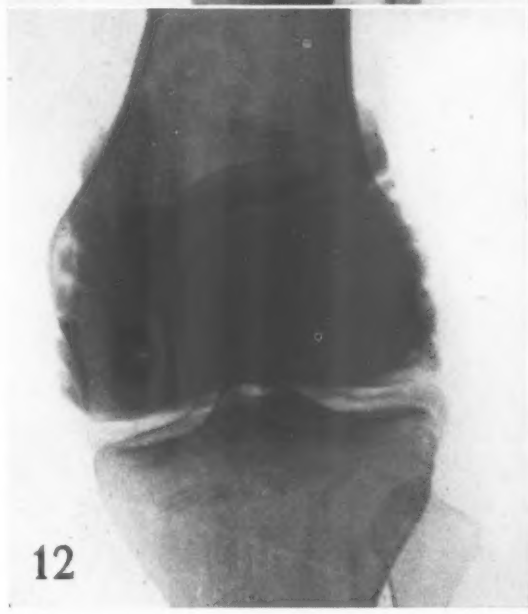
FIG. 6.—Normal arthrogram, boy aged seven years, antero-posterior view.

FIG. 7.—Normal arthrogram, boy aged seven years, lateral view.

FIG. 8.—Tear lateral meniscus, antero-posterior view.

FIG. 9.—Tear medial meniscus, internal rotation.



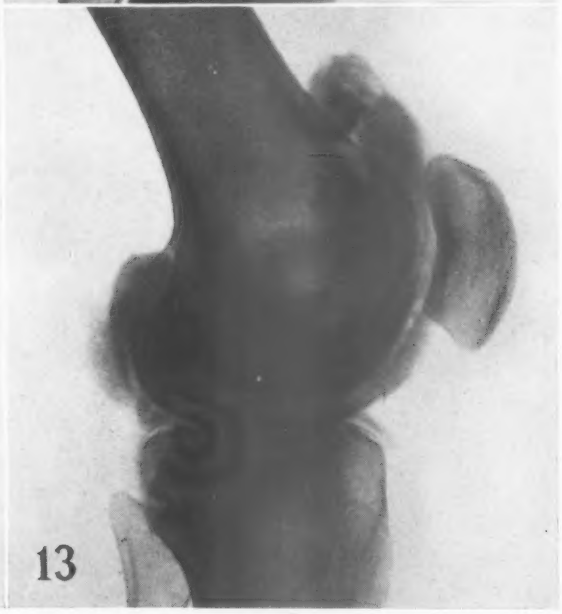




FIG. 10.—Villous arthritis (pre-operative) antero-posterior view.

FIG. 11.—Villous arthritis (pre-operative) lateral view.

FIG. 12.—Villous arthritis (postoperative), antero-posterior view.

FIG. 13.—Villous arthritis (postoperative), lateral view.

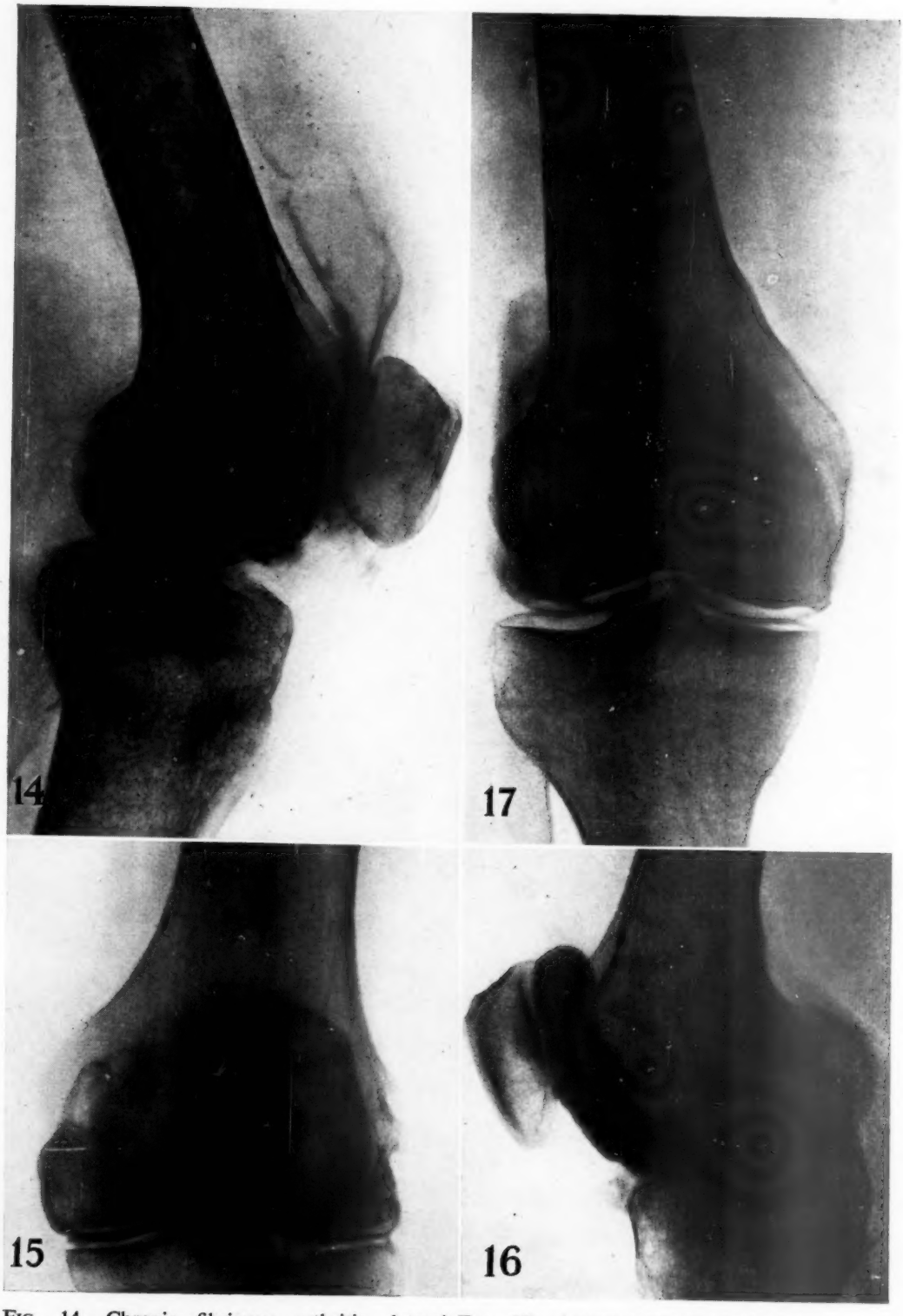



FIG. 14.—Chronic fibrinous arthritis, lateral view.

FIG. 15.—Old depressed fracture, lateral tibial condyle, lateral view.

FIG. 16.—Same case as Fig. 15, showing absent supra-patellar pouch, lateral view.

FIG. 17.—Antero-posterior arthrogram of a case of early osteo-arthritis.

shows how a defect in the lateral tibial condyle has been filled in, probably by fibrous tissue, the actual joint surface, as defined by the opaque medium, being regular and smooth. The menisci had been removed at operation soon after the injury. Fig. 16 shows that the synovial lining of the knee joint does not extend for more than a quarter of an inch above the patella : a well-filled posterior pouch is seen.

Fig. 17 illustrates a case of early osteo-arthritis. Osteophytes, which are seen at the edges of both femoral and the medial tibial condyles, do not yet encroach upon the joint space as demonstrated by the film of opaque medium. The articular cartilage is elsewhere smooth and of normal thickness. The menisci appear normal. The suprapatellar pouch is small.

### Possibilities for the Future

At present little is known about opaque arthrography of the knee, but it is expected that, as it becomes more widely used, improvements in technique and, particularly, in the interpretation of results will appear. It is a simple procedure, requiring no specialized apparatus or technique, and with proper care it appears to be safe. It is not, however, without its limitations, as in one recent case where a patient had a peripheral detachment of more than half of his medial meniscus, subsequently proved at operation, and yet no shadow suggestive of this was seen in the arthrograms.

### Summary

The technique of opaque arthrography of the knee is described, and its wider employment than has been usual heretofore is suggested.

The appearances of normal and of some abnormal arthrograms are described and illustrated.

I am indebted to the staffs of the hospitals concerned for much help, and I wish particularly to thank Mr. Norman Capener who initiated this work and who has given continuous help and advice.

#### References

Cullen, C. H., and Chance, G. Q. (1943). *Brit. J. Surg.*, **30**, 241.
Lagergren, K. A. (1934). *Acta Chirurg. Scand.*, **75**, 485.
Leveuf, J., and Bertrand, P. (1937). *Presse Méd.*, **45**, 437.
Severin, E. (1939). *J. Bone J. Surg.*, **21**, 304.
Sievers, R. (1926-7). Quoted by Severin.
Somerville, E. W. (1946). *J. Bone Jt. Surg.*, **28**, 451.

### Arthrographie Opaque de l'Articulation du Genou

#### Résumé

L'auteur décrit la technique de l'arthrographie opaque du genou, et pense qu'elle devrait être employée plus souvent qu'elle ne l'est actuellement. Il décrit et illustre les aspects des arthrographies normales et de quelques arthrographies anormales.

# RHEUMATOID ARTHRITIS AND AMYLOID DISEASE

BY

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This paper is a continuation of that by Lush, Chalmers, and Fletcher in the *Annals of the Rheumatic Diseases* for December 1948, vol. 7, p. 225, and reports a follow-up study of the case therein described.

### Progress of the Patient since the Report in December 1948

Just over three hundred days after the onset of the patient's illness and while she was still in the Royal Free Hospital she suddenly developed a rigor just after getting into bed. There were no premonitory symptoms or signs. Her temperature rapidly rose to 104·6° F. and the pulse to 130 per minute. Her only complaints were of pain over the sacrum and in the region of the left knee. Apart from the fever, tachycardia, and collapsed condition, no new physical signs were elicited. The blood pressure was 100/50 mm. Hg. The blood picture was unusual (white cells 9,000 per c.mm. of blood ; polymorphs 93 per cent., lymphocytes 7 per cent.), but no explanation for it could be found, and at the next examination it was more normal (white cells 7,700 per c.mm. ; polymorphs 38 per cent., lymphocytes 41 per cent., monocytes 13 per cent., eosinophils 5 per cent., basophils 3 per cent.). The urine contained a trace of protein and a few pus cells, but was sterile on culture.

No satisfactory explanation of the cause of this febrile attack was forthcoming. Infection was considered to be a possibility, and in view of her desperate condition it was considered justifiable to give the patient a course of penicillin, although this might obscure the diagnosis ; 250,000 units were given twice daily without demonstrable effect. For four days she remained shocked and ran a hectic fever ; then her condition slowly and spontaneously subsided. Two weeks after the onset of the episode she said she felt far better in every way than she did before the attack. Her condition never again gave any cause for anxiety, and she was discharged from the hospital shortly afterwards. At that time she was almost free from pain and was able to walk without assistance. The liver and spleen remained slightly enlarged.

### Condition after Discharge from Hospital

For subsequent news of her progress we are indebted to the patient herself, to Dr. H. F. G. Hensel of Blandford, Dorset, and to Drs. E. H. Shaw and K. I. Scott of Northampton General Hospital.

On June 14, 1948 (three months after her discharge), Dr. Hensel wrote : " You will be glad to hear that since she came home she has remained free from pain and has put on 9 lb. in weight and is altogether much better. As you suggested, I am giving her 4 c.cm. of Plexan per month. I notice that you suggested also 10 mg. of calcium aurothiomalate weekly. I gave this twice, but she produced an albuminuria and a metallic taste in the mouth. I tested the urine twice during the week and produced a heavy cloud of albumin each time, so I have had to stop it."

In reply to a later letter, Dr. Hensel wrote as follows on Oct. 21 : " Mrs. —— recently developed an acute tonsillitis which caused a slight flare up of her arthritis. She responded, however, to intensive penicillin therapy, the liver injections being maintained throughout. Afterwards I suggested a change, and she went away to Oxfordshire where she made wonderful progress. On her return to Dorset she relapsed again, with more swelling of the wrists and fingers and much pain. She assures me that there is no psychological association here and cannot account for the original onset of the trouble here, or of the present slight relapse.

" I have advised her to go back to Oxfordshire and have promised to try and help her husband to get a job and a farm cottage there. She has promised that she will come down to London to report to you when she is due."

Three weeks later, in normal handwriting, the patient herself replied as follows to a request to visit the hospital for a follow-up examination : " I am writing to tell you that I have had an attack of pleurisy and slight effusion, but I saw my doctor yesterday and he thought that I should be able to travel in a fortnight's time."

### Patient's Last Illness and Death

The patient recovered sufficiently to travel to Northampton to see her sister, but was almost immediately taken ill with severe pain in the chest. She was admitted to the General Hospital under the care of Dr. E. H. Shaw, whose house physician, Dr. K. I. Scott, wrote :

" This lady was admitted to Hospital on Nov. 20, 1948, with a complaint of severe pains in the chest of six days' duration. Following discharge from the Royal Free Hospital in May of this year she had been feeling very well, although a week or two after discharge she had some pain in the knee joints and hands. In September she moved to Brackley, hoping that the climate would suit her. She did well there but her pain recurred when she returned to Bournemouth six weeks later. She went back to Brackley, and in mid-November developed a pain below the left ribs which was worse on breathing. There was no pain in her chest or shoulder. The pain lasted for fourteen days, during which time she ran a slight temperature. She had no vomiting or headache. A diagnosis of pleurisy was made. She then developed a pain across the front of her chest which went through to the back. She described it as a griping pain, like indigestion. It was not affected by food, but was eased by taking tablets. The pain lasted for a day or two and made breathing difficult. She had

not lost any weight. The pain continued to recur at intervals of a day or so up to the day of admission. She had no cough and no urinary symptoms. She had noticed no swelling of the abdomen and her bowels were regular. On admission she looked very ill, was pale and sweating. The tongue was furred, the pulse regular, 130 per minute, blood pressure 120/90 mm. Hg., and heart sounds normal. Examination of the chest showed the signs of a pleural effusion at the left base. The abdomen was somewhat distended and she appeared to have marked enlargement of both liver and spleen. A radiograph of the chest confirmed the presence of a large left pleural effusion. The blood urea was 70 mg. and the blood sedimentation rate 105 mm. per hour. Examination of the blood showed 44 per cent. haemoglobin, 2,400,000 red cells per c.mm. of blood, and 9,000 white cells per c.mm. (74 per cent. polymorphs). Blood films showed marked anisocytosis and hypochromasia. Aspiration of the pleural effusion was attempted, but only 7 c.cm. of heavily blood-stained fluid were withdrawn. Sternal puncture showed a normoblastic marrow with no significant changes in cytology. A fractional test meal showed a complete histamine-fast achlorhydria.

A transfusion of 2 pints of blood was given on Nov. 28, 1948, and the haemoglobin rose to 74 per cent. Examination of the chest a fortnight later showed dullness of both lung bases, and 40 c.cm. of blood-stained fluid was withdrawn from the right pleural cavity. On repeated examination of the abdomen it was finally established that what appeared to be splenic enlargement was, in fact, gross enlargement of the liver, which extended to the level of the umbilicus and filled the epigastrium. The patient gradually developed a yellowish-brown pigmentation of the skin. Urine and stools remained normal in colour, and the sclera were not at first affected.

A provisional diagnosis of amyloid disease was made. Investigations of liver function were reported as follows: plasma proteins: albumin 0·9 per cent., globulin 3·9 per cent., total protein 4·8 per cent.; plasma bilirubin 1·5 per cent.; thymol turbidity 9 units; serum alkaline phosphatase 36 units.

The patient's temperature on admission had been 101·4° F., and she was started on a course of penicillin, 300,000 units twice a day. Her temperature settled during the next two days, but after that continued to vary between 97° and 99° F. On Dec. 11, 1948, the patient complained of severe pain centred round the left costal margin in the anterior axillary line. On examination the spleen could not be felt, the liver edge was three fingers' breadth below the right costal margin, and the abdomen was less distended than formerly. Peristalsis was normal, and there was no free fluid. Examination of the urine was negative. Her white cell count was 24,900 per c.mm. of blood with 91 per cent. polymorphs, and serum bilirubin was 2·2 per cent. A radiograph of the chest showed elevation of the right diaphragm, but the lung fields were clearer. During the next few days she continued to have left-sided pain, and her general condition deteriorated. On Dec. 14, 1948, she showed slight jaundice of the sclera. Her temperature continued irregular but not high, and her pulse remained about 90 to 100 per minute. Her respiration rate remained normal. She had a minor degree of albuminuria, although less than on admission. On the evening of Dec. 15, 1948, she had a very severe attack of pain across the abdomen. The upper abdomen was filled with a smooth, firm, and tender liver. No other abnormality was found in the abdomen. Her condition continued to worsen and she died at 7.30 the following morning. Permission to perform a necropsy was not given."

## Discussion

Unless a third concurrent disease was missed, this case must be classified as of fatal rheumatoid arthritis, for there were only sixteen months between the onset of the disease in a previously healthy woman and her death. Amyloidosis was diagnosed seven months after the first symptom of rheumatoid arthritis.

The cause of the pyrexia at various times was never explained, and she exhibited leucocytosis only in the last stages of her illness. The almost complete remission of symptoms, first on treatment with crude liver extract and secondly when she had a change of location is interesting, but its significance is difficult to assess. The most probable cause of the pleural effusions would be cardiac failure due to amyloid involvement of the myocardium, which would also explain the rapid terminal enlargement of the liver. There was evidence of both hepatic and renal failure towards the end, as would be expected in amyloidosis. Perhaps the severe anaemia occurring while the patient was on liver and iron therapy was due to amyloid involvement of the bone marrow. It will be noted that, contrary to expectation, the albuminuria was never very gross. The incredibly low level of the serum albumin cannot readily be explained. The pigmentation of the skin, occurring independently of jaundice or ultra-violet ray therapy, remains yet another mystery.

It is a pleasure to acknowledge our debt to Dr. Hensel for his keen interest in the progress of his case and his helpful reports thereon, and to Drs. Shaw and Scott for their information about the last stages of the disease.

## Arthrite Rhumatismale et Maladie Amyloide

RÉSUMÉ

Dans le numéro de décembre 1948 des *Annals of the Rheumatic Diseases*, 7, 225, Lush, Chalmers, et Fletcher avaient décrit un cas d'arthrite rhumatismale et de maladie amyloïde; maintenant ils donnent la suite de l'étude du cas précédemment décrit allant jusqu'à la mort de la malade.

A moins qu'une troisième maladie no décelée n'ait été présente, ce cas doit être classé comme un cas mortel d'arthrite rhumatismale, car il ne s'ést écoulé que seize mois entre le début de la maladie chez cette femme jusque là bien portante et sa mort. La maladie amyloïde a été diagnostiquée sept mois après l'apparition du premier symptome d'arthrite rhumatismale.

# GENERALIZED MYOSITIS FIBROSA: CASE REPORT

BY

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Generalized myositis fibrosa is rare, and its clinical appearance and behaviour are so well defined that it is considered justifiable to report a case recently observed.

### Case Report

The patient, a single woman aged fifty-four years, had worked for four years as a radio-condenser assembler. She had had asthma from 1930 to 1941 for which she had been treated by an autogenous *Streptococcus viridans* vaccine prepared from a nasal swab, with improvement of symptoms. Skin tests against animal fluffs and food proteins had all been negative. All her teeth were removed for pyorrhoea alveolaris in about 1930. For six months previous to observation she had suffered intermittently from iritis in the left eye. She had never been abroad, did not smoke, and took alcohol only occasionally.

**Family History.**—Her mother died at the age of sixty-eight, having had rheumatoid arthritis for many years, and her father at the age of seventy-two from bronchitis and asthma.

**Patient's History.**—About five years ago she first noticed pain in the soles of her feet when walking, which she attributed to "high arches", and about a year later she consulted an orthopaedic surgeon, who arranged for her to have suitable boots. These made walking more comfortable, but her feet continued to "curl up", until she was quite unable to walk without the aid of her surgical boots. About twelve months before she was seen she began to feel unusually tired, and a little later she noticed that her fingers were beginning to curl up; they were painful when she woke up and when they were in use. Apart from this her general health was good. The menopause had occurred eighteen months before. She appeared well nourished and was mentally well adjusted to her disability. She remained afebrile during the three weeks in which she was in hospital. The left pupil was smaller than the right and slightly irregular in outline; both reacted to accommodation, the right directly and consensually to light, and the left to neither light stimulus. A small foreign body was removed from the left cornea. When dilated by homatropine the left iris showed posterior synechia. The fundi were normal.

There was moderate limitation of flexion and extension of the fingers of both hands, but no evidence of involvement of the joints concerned: wrist movements were full and free with the fingers partially flexed. Passive extension of the wrist caused flexion of the fingers, and vice versa. The extensor and flexor groups of muscles of both forearms felt firmer than is normal, having the texture of a muscle in spasm, though this was evidently not the cause of the induration. The small muscles of the hand appeared normal. There was marked equinus and cavus deformity of the feet, with hallux valgus and hammer toes, so that when the patient tried to walk the metacarpals were placed almost vertically, the anterior part of the foot being acutely plantar flexed on the talus (see illustration). This deformity had evidently arisen as a result of simultaneous contracture of the toe flexors and extensors. The tendo achillis was also markedly shortened, and there was minimal movement in the ankle joint and all the joints distally. The calf muscles appeared wasted (R> L) and all the leg muscles felt indurated. Hip and knee movements were normal, and there were no skin changes.

The respiratory, cardiovascular, alimentary, and genito-urinary systems were clinically normal; the nervous system showed only the pupillary changes noted, with absent ankle jerks and plantar responses which were accounted for by the deformity present.

Muscle biopsy from the left flexor digitorum profundus had been performed six weeks earlier. Sections from the tissue excised showed some fibres thinner than normal, with diminution of striation, collections of nuclei between muscle fibres, and some small round-celled infiltration. No evidence of fibrosis was found in the sections examined from this biopsy, and it was not considered justifiable to repeat the procedure in order to confirm the fibrosis.

**Special Investigations.**—The following further investigations were made. A radiograph of the cervical and lumbar spine showed slight osteo-arthritic changes. Radiographs of the arms and legs showed only the deformities described; there was no evidence of abnormal calcification in the soft tissues. A chest radiograph showed mild emphysema and a radiologically normal heart. The cerebrospinal fluid was normal.

The Wassermann reaction was negative in the blood and cerebrospinal fluid. The blood count was: Hb 100 per cent. red cells 5·4 million per c.mm. of blood, colour index 0·9, white cells 7,000 per c.mm., polymorphs 61 per cent., eosinophils 8 per cent., basophils 1 per cent., monocytes 12 per cent., lymphocytes 18 per cent.

The sedimentation rate was 15 mm. in the first hour (Westergren).

Plasma inorganic phosphorus was 4·6 mg. per 100 ml.

Radiograph of one foot of the patient here described. The appearance in the other foot was almost identical.

of blood, calcium 10 mg. per 100 ml., potassium 24 mg., and uric acid 2·9 mg. A twenty-four-hour specimen of urine contained 110 mg. of creatine and 274 mg. of creatinine.

The electrocardiogram and electrical reactions were normal.

## Discussion

From a review of the literature it would appear that the condition is rare ; it is difficult to determine the precise number of cases recorded, as some are inadequately described and in some the diagnostic criteria are not completely satisfied, but it would appear to be about thirteen.

Burton and others (1923-4) reviewed the cases previously described, accepted five as being generalized as opposed to the localized form of myositis fibrosa, and added one of their own. They reported the progress of their case after eight years, after a prolonged remission (Burton and others, 1931). Ornsteen (1935) reported the condition in a forty-two-year-old male in whom the spinal muscles were principally affected. The case superficially suggested a form of myotonia, but biopsy showed the usual histological changes of myositis fibrosa.

Blau (1938), in a full review, accepted eight previous cases and added two of his own.

Somers (1939) reported a patient who had suffered from asthma which had been relieved by removal of nasal polypi.

Ellerman (1943) reported a case in which the skin was adherent over many of the widely scattered but relatively localized muscle lesions.

Benedek (1944), under the title pseudomyasthenic syndrome in polymyositis interstitialis chronica fibrosa, described a case which clinically resembled myasthenia, but showed the histological changes of myositis fibrosa.

Aetiologically no factor can be recognized which is in any way constant for these cases. Diagnosis is based on the clinical behaviour of the condition and the biopsy findings. Its onset is insidious, usually with stiffness affecting the legs, arms, or back, and its course chronic, progressing to contractures in the groups of muscles affected, with coincident wasting. Further progress may be prolonged through a series of remissions and exacerbations extending over many years. Pain is absent, the pain in the case here reported being due to the foot deformity rather than directly to the condition in the muscles.

The affected groups of muscles are characteristically indurated, and impart a sensation to the observer variously described as " doughy ", " boggy ", " firm ", " like a sandbag ". It may spread widely to affect practically the entire muscular system, though the face is spared. The skin usually remains normal throughout its course., thus distinguishing it from dermatomyositis, which in the earlier stages is the most likely differential diagnosis. The course is afebrile. Degenerative, inflammatory, and fibrotic changes are found histologically in muscle biopsies from affected areas. Hyaline and vacuolar degeneration may be seen in muscle fibres, which often appear granular and structureless with loss of striation. Round-celled infiltration is found round degenerating fibres, and fibrous tissue replacement is found in the more advanced lesions.

Bodansky and others (1929-30) investigated the creatine and creatinine metabolism fully in their patient, a negro boy of fourteen years who also suffered from pulmonary tuberculosis. The age and coincident disease in this case would render their conclusions questionable, but they demonstrated an inability to retain exogenous creatine ; 40 per cent. of the total creatine and creatinine was excreted as creatine.

It is considered most likely that the iritis in the case here reported was due to the presence of a foreign body and was not connected aetiologically with the general disease process.

Treatment has usually been conservative and confined to measures designed to maintain and improve function in the affected groups of muscles. Drug therapy has produced no significant benefit, and

Somers (1939) manipulated his patient, who died shortly afterwards from what was thought to be coronary occlusion.

**Summary**

A case of generalized myositis fibrosa is reported. The subject is briefly reviewed.

I wish to thank Dr. G. L. S. Konstam, under whose care the case was observed, for permission to report it ; Dr. B. Buckley Sharp for the biopsy sections, and Mr. H. G. Blunt for the reproduction of the *x*-ray photograph.

REFERENCES

Benedek, L. (1944). *Mschr. Psychiat. Neurol.*, **109**, 93.
Blau, A. (1938). *J. Mt Sinai Hosp.*, **5**, 432.
Bodansky, M., Schwab, E. H., and Brindley, P. (1929-30). *J. biol. Chem.*, **85**, 307.
Burton, J. A. G., Cowan, J., and Fleming, J. (1931). *Quart. J. Med.*, **24**, 369.
——, ——, and Miller, H. (1923-4). *Ibid.*, **17**, 103.
Ellermann, M. (1943). *Acta psychiat., Kbh.* **18**, 411.
Ornsteen, A. M. (1935). *Ann. Surg.*, **101**, 237.
Schwab, E. H., Brindley, P., Bodansky, M., and Harris, T. H. (1932). *Ann. intern. Med.*, **6**, 422.
Somers, D. C. (1939). *J. Bone Jt. Surg.*, **21**, 414.

**Myosite Fibreuse Généralisée : Observation**

RÉSUMÉ

Environ treize cas de myosite fibreuse généralisée ont été rapportés dans la littérature. L'auteur de cet article en décrit un quatorzième : la malade est une femme célibataire âgée de 54 ans, qui a travaillé pendant quatre ans à l'assemblage de condensateurs de radio. Elle a été atteinte d'asthme et d'iritis. La maladie a affecté les doigts des deux mains, les muscles des avant-bras, les pieds, et les muscles des mollets. Le sujet est passé en revue brièvement.

# ABSTRACTS

*[This section of the* ANNALS *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; general pathological articles; other general articles. At the end is a list of articles that have been noted but not abstracted. Not all sections may be represented in any one issue.]*

## Acute Rheumatism

**Coronary Lesions in Acute Rheumatism.** (Les lésions coronaires du rhumatisme articulaire aigu.) DE BRUX, J. (1948). *Ann. Méd.*, **49**, 278.

This is a somewhat procrustean attempt to fit the changes in the coronary arteries, as found in some cases of acute rheumatic disease, into the three stadia described by Klinge. The changes described here are those of the rheumatic process, not the precocious atheroma, which is rare despite the cardiologists who quote it so often. The author also refuses to follow the fashion of saying that this is just a variant of polyarteritis nodosa (Kussmaul). He emphasizes [rightly] that varying degrees of myocardial infarction are not infrequently revealed on microscopy of the rheumatic heart, a fact that has not been widely appreciated. He discusses the appearances in the coronaries in the light of recent work on experimental hyperergic lesions. *A. C. Lendrum.*

**The Value of Roentgenography in the Diagnosing of Cardiac Disorder following Rheumatic Fever.** [In English.] HANSSON, C. J., and JACOBSSON, E. (1948). *Acta radiol. Stockh.*, **29**, 541.

This paper is based on the correlation of the radiographic and clinical findings in the course of a follow-up in 1944-45 of 494 patients who, as children, had one or more attacks of rheumatic fever. In nearly 22% of the cases the radiographic findings were important for deciding the diagnosis and prognosis.

**The Diagnosis of Mitral Insufficiency in Rheumatic Children.** KUTTNER, A. G., and MARKOWITZ, M. (1948). *Amer. Heart. J.*, **35**, 718.

In order to assess the importance in rheumatic children of a loud blowing systolic murmur in the absence of demonstrable cardiac enlargement a comparison was made of the after-history of 144 children having such a murmur with that of 171 similar patients with potential and possible heart disease but with not more than a soft systolic murmur.

The observations suggest that the diagnosis of mitral insufficiency, based on a loud blowing apical systolic murmur, is justified in children and carries a grave prognostic significance. *H. E. Holling.*

**The First Ten Years of Rheumatic Infection in Childhood.** ASH, R. (1948). *Amer. Heart J.*, **36**, 89.

The author analyses a follow-up study of 547 children observed for 10 years after the onset of rheumatic fever. At the end of the 10-year period over 90% of the group had been located. At the end of the initial attack 41% gave no evidence of heart disease ; of these, over 76 still showed no evidence of heart disease at the end of 10 years, while only 5% had died of rheumatic infection or bacterial endocarditis. Over 40% of children with rheumatic heart disease in the first attack had died by the end of 10 years of rheumatic infection or bacterial endocarditis, while in just under 10% the signs of cardiac involvement had disappeared. The results agree with

the larger group reported by Jones and Bland (*Trans. Ass. Amer. Phys.*, 1942, **57**, 265). *R. J. Grant.*

**Rheumatic Fever in Childhood.** WESTON, W. (1948). *J. Amer. med. Ass.*, **137**, 675.

The clinical manifestations, differential diagnosis, pathology, and treatment of rheumatic fever in childhood are described. The author advocates a scheme for detection, investigation, and follow-up of cases on the lines of the anti-tuberculosis schemes and thinks that rheumatic fever should be a notifiable disease.

**The Course of Acute Rheumatism in Children in War and in the Post-war Period.** (Течение ревматизма у детей в годы войны и послевоенный период). KOVALEVA, E. V. (1948). *Pediatriya*, No. 4, 13.

In a Moscow clinic a remarkable lowering in the incidence of acute rheumatism in children was observed during the war, and the course of the disease became milder (5·9% mortality rate, against 14·6% in peace time). The incidence of pericarditis fell. In 33% of wartime cases leucopenia was present, and in 60% anaemia. Since the end of the war the incidence of acute rheumatism has risen sharply, from 4·6% of all admissions in 1942 to 18% in 1947, and the disease has again become more severe. Severe exudative reaction is now commoner—polyserositis, polyarthritis, pneumonia—but the mortality rate remains low (4·5%). Nevertheless in the more severe cases there is a tendency to early death, within 2 to 3 months of the onset of the disease, and sometimes earlier. *S. S. B. Gilder.*

**Salicylate Therapy in Children.** MAGGIONI, G. F. (1948). *Arch. Dis. Childh.*, **23**, 40.

The author has investigated the absorption and excretion of sodium salicylate and " aspirin " given orally and per rectum to rheumatic and non-rheumatic children. He showed that a large dose is excreted more slowly than a small one. A steady blood level of at least 25 mg. per 100 ml. is given by a daily dosage of 1 to 1·5 gr. per lb. of body weight. He confirmed the fact that sodium bicarbonate increases the urinary excretion of salicylates. When administration was stopped even after many weeks' treatment the drug disappeared from the blood and urine in 48 to 72 hours. *R. S. Illingworth.*

**Investigations of the Salicyclic Acid Reaction in Acute Rheumatism.** (Untersuchungen über die Salicylsäure-reaktion in der Rheumadiagnostik.) HEINSEN, H. A. (1948). *Dtsch. Arch. klin. Med.*, **193**, 247.

The author investigated the activity or otherwise of rheumatic heart disease with the aid of Schroeder's modification of Mester's test (*Z. Rheumaforsch.* 1942, **5**, 377).

**Treatment of Rheumatic Fever with Sodium Salicylate and Ammonium Chloride.** (Tratamiento de la fiebre reumatica con salicilato de sodio y cloruro de amonio.) PASQUALINI, R. Q., and LASCALEA, M. C. (1948). *Prensa méd. argent.*, **35**, 1091.

Thirty-five cases of acute rheumatism in young adults were treated by the following method. Isotonic solutions of sodium salicylate (2·32%) and ammonium chloride (0·82%) were prepared and mixed in the proportion of 750 ml. of the former to 500 ml. of the latter. The mixture was introduced by rectal drip at a rate of 35 drops a minute for 2-hour periods with intervals of 2 hours. An evacuant enema was previously given. Treatment continued for from 1 to 15 days; each 24 hours 17·4 g. of sodium salicylate and 4·1 g. of ammonium chloride were given in this manner. The rectal drip was discontinued when the temperature had been normal for 24 hours, and salicylate was then given by mouth in doses of 1 g. 2-hourly until the erythrocyte sedimentation rate became normal. A smaller dose was then administered for several months.

In all cases but one, pain was relieved within 24 hours; the temperature became normal within this period in 8 cases, within 2 days in 7, and within 3 days in 9. The erythrocyte sedimentation rate fell to normal more rapidly with this treatment than in cases treated with salicylates alone. In 7 cases of exudative pericarditis the result was particularly satisfactory. No signs of local irritation or of toxicity were observed. *S. S. B. Gilder.*

**Does Sodium Salicylate Cure Rheumatic Fever?** REID, J. (1948). *Quart. J. Med.*, **17**, 139.

To answer the question contained in the title the author studied 12 patients; 9 adults had polyarthritis, fever, and tachycardia; 3 children had pericarditis, fever, and tachycardia.

Plasma salicylate levels of 20 to 46 mg. per 100 ml. were reached in 3 to 8 days, then a fall occurred. Higher levels were reached and maintained without added sodium bicarbonate, probably due to less urinary excretion. At the highest plasma salicylate levels there was depression of alkali reserve and urine *p*H. The author concludes that the rate of disappearance of pain, fever, and tachycardia and the rate of fall in the erythrocyte sedimentation rate are proportional to the height of the plasma salicylate level. In one case it is even claimed that pericardial friction disappeared and reappeared with rise and fall respectively in salicylate level. [No electrocardiographic evidence of pericarditis is offered, and since the patient was febrile when friction was heard it is conceivable that this was due to a dilated pulmonary artery as suggested by Ortiz (*Arch. lat.-amer. Cardiol. y Haematol.*, 1933, 3, 45).] The author thinks that plasma salicylate levels should be kept between 30 and 40 mg. per 100 ml. while disease is active.

[The absence of controls is conspicuous. The observations are scanty. From the evidence offered, no anti-streptolysin titres were estimated. From the few maximum and minimum levels given, it is not possible to form an estimate of plasma salicylate levels throughout the 24 hours. Erythrocyte sedimentation rates were estimated on oxalated blood without dilution. This is a novel and possibly unreliable method. Further, it would be of interest to know what effect, if any, salicylate has directly on the E.S.R. of a blood sample.] *G. Loewi.*

**The Salicylate Level in the Blood as the Basis of Treatment in Acute Rheumatic Endocarditis. Effect of Sodium Bicarbonate and Benzoate.** (La observación de la salicilemia como base del tratamiento de las endocarditis agudas reumáticas. Efectos del bicarbonato y benzoato sódicos.) ARJONA, E., ALES, J. M., and SEGOVIA, J. M. (1948). *Rev. clin. esp.*, **28**, 92.

The salicylate level in the blood was determined by a method previously described (*Rev. clin. esp.*, 1947, **27**, 21). A single oral dose of 2 g. of sodium salicylate

and 2 g. of sodium bicarbonate produces a maximum concentration in the blood within the first hour, varying from 10 mg. to 25 mg. per 100 ml., according to the individual. This concentration remains nearly stationary for the next 4 hours. Rectal introduction of 8 g. of sodium salicylate causes the level to rise above 35 mg. per 100 ml. within 4 hours and to be maintained for 24 hours. A further enema of 8 g. at the end of 24 hours raises the level above 50 mg. per 100 ml. The rise in the salicylate level in the blood is hampered by the addition of bicarbonate, and an effective concentration (25 to 35 mg. per 100 ml.) often cannot be reached even with a daily dose of 10 g. of salicylate. If sodium benzoate is substituted for the bicarbonate a dose of 10 g. of salicylate is always sufficient to raise the level above 35 mg. per 100 ml. Contrary to the claim of a previous author, *p*-aminobenzoic acid does not yield any better results than sodium benzoate, in association with salicylate.

Pending a further study of the problem, the authors provisionally advise the administration of salicylate and benzoate together either orally—8 g. daily for 2 to 3 days, followed by 4 to 6 g. daily, or rectally—8 g. on the first day, followed by 4 to 6 g. daily. *A. Lilker.*

**Succinate Therapy in Acute Rheumatic Fever.** WEGRIA, R., FISCHEL, E. E., and WILSON, P. E. (1948). *New Engl. J. Med.*, **239**, 117.

The authors conclude that neither the natural course of rheumatic fever nor its signs and symptoms were modified by "subenon", which has elsewhere been favourably reported on as a therapeutic agent. ("Subenon" is the calcium double salt of benzoic acid and succinic acid benzyl esters.)

**Rheumatic Fever: p-Aminobenzoic Acid.** (Fiévre rhumatismale : acide para-aminobenzoique.) BÉLISLE, M. (1948). *Un méd. Can.*, **77**, 392.

It was reported in 1946 that if *para*-aminobenzoic acid were administered by mouth to patients undergoing sodium salicylate therapy, a rise in the salicylate level of the blood was provoked. Three cases are now reported in which this observation is confirmed.

## Chronic Articular Rheumatism (Rheumatoid Arthritis)

**The Heart in Rheumatoid Arthritis.** FISCHMANN, E. J., and GWYNNE, F. J. (1948). *Brit. Heart J.*, **10**, 125.

The authors studied 60 patients suffering from rheumatoid arthritis selected from 150 on the basis of three criteria : (1) they were able to stand up ; (2) they were not hypertensive ; (3) they had no history of rheumatic fever. The majority, if not all, were anaemic. Only one patient had a mitral diastolic murmur. The electrocardiogram showed a tendency to low voltage, but nothing else significant. Cardiac enlargement, mostly left ventricular, was found on *x*-ray examination in 23% of cases, and was attributed to chronic rheumatic carditis or to a previously unrecognized "form of cardiac involvement due to the aetiological factor of rheumatoid arthritis". [The authors do not appear to be familiar with the effects of anaemia upon the heart.] *Paul Wood.*

**Cardiac Lesions in Rheumatoid Arthritis.** (Artritis reumatoides y cardiopatias.) LOSADA, M., and FRANCE, O. (1948). *Rev. med. Chile*, **76**, 480.

Of 136 cases of rheumatoid arthritis, mitral lesions were found in 4, but the interpretation of the relation between arthritic and cardiac lesions is difficult, since (1) in 3 of the 4 patients there was some evidence of a previous acute rheumatic infection, and (2) necropsy examination of 200 patients without a history of rheumatism revealed stigmata of rheumatism in 80 hearts.
*S. S. B. Gilder.*

**Brucellosis as a Cause of Sacroiliac Arthritis. A Study of Its Relationship to Rheumatoid Spondylitis.** STEINBERG, C. L. (1948). *J. Amer. med. Ass.*, **138**, 15.

After an outline of the present-day incidence of *Brucella abortus* infection in man and cattle in the U.S.A., the literature on rheumatic (arthralgic) manifestations of brucellosis is reviewed. It is noted that, though sacro-iliac arthritis has been cited as a complication of undulant fever, no case report has been found after careful search. A report is given of a case of sacro-iliac arthritis with destructive changes in one joint in a patient showing clinical and serological evidence of recurrent *Br. abortus* infection. Partial healing had occurred, and no evidence of true ankylosis was seen. The results of limited streptomycin therapy were considered to be inconclusive. The possibility that *Br. abortus* infection is an aetiological factor in rheumatoid spondylitis is discussed, but the two syndromes are held to be unrelated. Twenty cases of rheumatoid spondylitis are reviewed ; no significant relation to *Br. abortus* infection is demonstrated in these cases. *K. M. Lawther.*

**Amyloidosis in Rheumatoid Arthritis. A Report of Ten Cases.** UNGER, P. N., ZUCKERBROD, M., BECK, G. J., and STEELE, J. M. (1948). *Amer. J. med. Sci.*, **216**, 51.

Four cases of amyloid disease were found at necropsy in 58 cases of rheumatoid arthritis. Liver, spleen, and kidney were affected in each case, and adrenals, pancreas, and heart in 1. The duration of the arthritis was from 8 to 23 years and the severity of the disease was not different from that in non-amyloid cases. A search for amyloidosis was then made among 56 patients and was found in 6. In only 1 patient, in whom tuberculosis had been arrested for 8 years, was any possible cause for the amyloid disease found other than rheumatoid arthritis.

**Rheumatoid Arthritis after Injury to a Single Joint.** KELLY, M. (1948). *Med. J. Aust.*, **2**, 309.

Ten cases are reported in which injury to a single joint was followed by chronic polyarthritis in patients previously free from rheumatic conditions. The times of onset of polyarthritis after the injuries varied from a few weeks to several months, and there was a tendency for the condition to spread symmetrically. The order of joint involvement is tabulated, together with similar data in three other groups of cases. It is held that there is no evidence that these patients were already predisposed to this disease and that the non-articular trauma was the "only visible causative factor" in the development of polyarthritis in these cases.
*K. M. Lawther.*

**Iron and Copper Content of the Blood Serum in Chronic Infectious Polyarthritis.** (Om Jern og Kobbers Forekomst i Blodserum ved kroniske infektiose Polyarthritier.) BRENDSTRUP, P. (1948). *Ugesk.Læg.*, **110**, 948.

The author reviews the literature on the content of iron and copper in the blood in various diseases, and mentions

that infections, administration of diphtheria toxin in horses, and injection of blood or milk all produce a rise in the serum copper level and a fall in serum iron.

He describes his findings in 80 female and 40 male patients with active chronic infective arthritis ; about the same number in each sex had rheumatic fever as had infective polyarthritis, with a few cases of ankylosing spondylitis. Iron and copper were estimated by the methods described by Brendstrup (*Ugesk. Læg.*, 1948, **110**, 945). The iron content averaged 76 μg. per 100 ml. in women (range 19 to 153 μg.) and 89 μg. per 100 ml. (with the same range) in men ; the normal averages are 98 and 126 μg. per 100 ml. respectively. The copper content averaged 169 μg. per 100 ml. in women (range 82 to 310 μg.) and 141 μg. per 100 ml. in men (range 86 to 319) ; the normal averages are 120 and 113 μg. per 100 ml. respectively. If 165 μg. was taken as the upper limit of normal for serum copper, there was a good correlation between rise in copper values and rise in erythrocyte sedimentation rate and also between iron and copper values in individual patients. The correlation between abnormal erythrocyte sedimentation rates and lowered iron values was not so good. Clear tables and a diagram demonstrate these results. Heilmeyer considered the copper level a better guide to the activity of infection than the erythrocyte sedimentation rate ; the author thinks that both are equally useful.

*A. M. M. Wilson.*

**Still's Disease in Children.** (Болеэнь стилла у детей). SHAPIRO, G. B., and VILENKINA, O. Y. (1948). *Pediatriya*, No. 4, 35.

At the rheumatism clinic of the Children's Hospital, Moscow, 19 cases of chronic progressive multiple arthritis of unknown origin have been treated in the past 6 years. Analysis of these suggests that they are all cases of Still's disease. Sixteen of the children were taken ill before the age of 7, the earliest at 7 months old. There was no relation to acute infections. In 13 a clear picture of Still's disease developed.

## (Osteo-arthritis)

**Chronic Idiopathic Hypertrophic Osteo-arthropathy.** CAMP, J. D., and SCANLAN, R. L. (1948). *Radiology*, **50**, 581.

Chronic idiopathic hypertrophic osteo-arthropathy occurs predominantly in males at the age of puberty or adolescence and is characterized by the osteo-arthropathic syndrome—clubbing of the digits, enlargement of bones and joints, and thickening of the skin of the face. It shows a relation to puberty which suggests a constitutional disease made apparent by endocrine imbalance. The authors calculate that this form constitutes 3 to 5% of all cases. The disease has a familial tendency in 60% of cases, and a seasonal fluctuation. The features become coarse, the nose bulbous, the fingers clubbed. There is hypertrophy of the nipples, feminine distribution of hair, acne vulgaris, and excessive perspiration of the hands, feet, and axilla. The subcutaneous tissue is thickened. The extremities when dependent are cyanosed. Periosteal accretions are found on all tubular bones except the phalanges, whose terminal tufts are atrophied.

*James F. Brailsford.*

**Costo-transverse Arthrosis Deformans.** (L'artrosi deformante costo-transversaria). NICOLOSI, A. (1948). *Radiolog. med., Torino*, **34**, 348.

This work is based on the study of 377 radiographs of the chest, 277 of which showed evidence of pleuro-pulmonary tuberculous lesions, 100 being normal. The costo-transversal osteo-arthritis was not accompanied by osteo-arthritic changes in the spine at the same level, was at a higher level than the spinal osteo-arthritis, when such was present, was found mainly in men, and had no connexion with the pulmonary tuberculosis. *A. Orley.*

**Histological Studies of Osteo-arthritis of the Hip.** (Ricerche istologiche nell'artrosi deformante dell'anca). LUGIATO, P. (1948). *Chir. Organi Mov.*, **32**, 201.

The collagenous fibres of cartilage and of bone can be distinguished only with difficulty by the ordinary microscopical methods while with polarized light the details of fibrillar structure are easily seen as well as the disorders of their structure. The author examined the lining of the cartilaginous elements of the hip-joint in arthritis deformans, and found that the loss of elasticity is due to changes in the fibrillary structure of the birefringent fibrils.

**Treatment of Osteo-arthritis by Intra-articular Injections, with Special Reference to the Hip-joint.** (De behandeling van arthrosis deformans (in het bijzonder coxarthrosis) met intra-articulaire inspuitingen.) MENDES DE LEON, C. (1948). *Ned. Tijdschr. Geneesk.*, **92**, 2084.

Seven cases of osteo-arthritis of the hip-joint were treated by intra-articular injections of 10 ml. of a 2% procaine and 1% ascorbic acid solution. The patients were kept in bed for 3 to 4 weeks and often an elastic bandage was applied. As in-patients they received 2 to 3 injections a week, followed by weekly injections in the out-patient department for several weeks. The aims of the treatment were : (1) to relieve pain and vascular spasm by procaine ; (2) to maintain intra-articular acidity, as postulated by English workers (*p*H of the solution was 4·7 to 5·7) ; (3) to further intra-articular metabolism by means of the oxidation-reduction function of vitamin C. In all cases the clinical results were satisfactory ; pain disappeared, motility of the joint increased and the patients were able to resume their daily occupations. The technique of the injections deserves mention. The needle was introduced in the centre of a line joining the great trochanter and the femoral artery, felt under Poupart's ligament, and directed towards the femoral head, piercing the ilio-femoral ligament and its capsule. This technique is recommended as the easiest one.

*A. Lilker.*

**Open Reduction for Slipping of the Upper Femoral Epiphysis.** [In English.] FRIBERG, S. (1948). *Acta orthopaed. scand.*, **17**, 189.

For cases of slipped capital epiphysis of the femur in which less than two-thirds of the surfaces of the head and neck are in contact, the author prefers open reduction combined with nailing. The preliminary results are good, both subjectively and objectively, in 10 out of 12 cases ; the exceptions are a case with total necrosis of the head, and another where the reduction was unsatisfactory.

**On Complications Following Nailing Arthrodesis of the Hip-joint.** [In English.] KARLÉN, A. (1948). *Acta orthopaed. scand.*, **17**, 195.

The author gives an account of the results and complications following nailing arthrodesis of the hip-joint in 90 cases.

**Positive Pressure in Arthrodesis of the Knee Joint.** CHARNLEY, J. C. (1948). *J. Bone Jt Surg.*, **30B**, 478.

A method of arthrodesis of the knee-joint is described, by the use of which the author reduced the period of disability in 15 patients to 3 months.

**Arthrodesis of the Ankle Joint. Experiences with the Transfibular Approach.** ADAMS, J. C. (1948). *J. Bone Jt Surg.*, **30B**, 506.

The author describes a method of arthrodesis of the ankle in which the lower end of the fibula is used as a graft. In 28 cases fusion occurred on an average in thirteen weeks. *George Perkins.*

**Intramedullary Pinning for Arthrodesis of the Knee Joint.** CHAPCHAL, G. (1948). *J. Bone Jt Surg.*, **30A**, 728.

The author describes a method which has been used on 7 knees. Good results were achieved in 6, and in 1 the nail fractured. *J. S. Batchelor.*

**The Management of Destructive Arthritis of the Hip by Means of Intravenous Procaine.** GRAUBARD, D. J., KOVACS, J., and RITTER, H. H. (1948). *Ann. intern. Med.*, **28**, 1106.

A new treatment for destructive arthritis of the hip, designed to give immediate relief from pain, to relax muscular spasm round the hip, and to promote increased mobility, is described.

**Vertebral and Epiphyseal Chondrodysplasia.** (Chondrodysplasie spondyloepiphysaire). LAYANI, F., DUCROQUET, R., and POINSARD, G. (1948). *Rev. Rhum.*, **15**, 240.

A boy aged 11½ had suffered from lameness since starting to walk at the age of a year ; at 2½ years bilateral coxa vara was diagnosed. At 5 years he was placed in plaster, and at 7 years a bilateral subtrochanteric osteotomy was performed. The hip condition continued to progress, and when the boy was seen by the authors it was considered to be only one manifestation of a generalized bone dysplasia.

The authors discuss the relation of the condition to other bone dysplasias and dystrophies.

## (Spondylitis)

**Spondylarthritis Ankylopoietica.** (Spondylartritis anchylopoetica.) BRAHME, L. (1948). *Nord. Med.*, **39**, 1375.

The author reviews present knowledge of spondylitis ankylopoietica and discusses the condition with reference to his own experience and records of the disease in Sweden.

The author's material is taken from the Norrköping Hospital records for the last 20 years, during which 28 patients with ankylosing arthritis of the spine received 90 periods of treatment. They fall into two groups, with 14 cases in each. In the first condition, called by the author primary Bechterew's disease, there is a " bamboo spine " without joint deformation in the spine or, save rarely, elsewhere ; patients are between 20 and 40, with a peak incidence about the age of 30. In the other group (secondary Bechterew's disease) " bamboo spine " is never seen but there is deformative arthritis of the spine and also arthritis of the small joints in every case ; ages range from 20 to 50 and there is no peak incidence. The author believes that the latter condition represents one result of a generalized polyarthritis, and that, though cases are symptomatically indistinguishable from those in the primary group, the condition is aetiologically different and radiologically (if not clinically) distinguishable.

Apart from symptomatic treatment, gold is recommended for early cases and *x*-ray therapy as the most effective generally. In 3 cases with high serum-calcium values parathyroidectomy was carried out without objective benefit. Female sex-hormone therapy is also suggested. *A. M. M. Wilson.*

**Vertebral Osteotomy: Technique, Indications, and Results.** HERBERT, J. J. (1948). *J. Bone Jt Surg.*, **30A**, 680.

The author advocates that operative correction of the kyphotic deformity of the spine in ankylosing spondylitis should be accomplished in two stages : the neural arch is divided by a posterior approach and the bodies by a flank approach, with an interval of 2 to 3 weeks between the operations. Posterior and anterior osteotomy are described. The operation has been performed in 9 patients in 7 of whom anterior and posterior osteotomy proved necessary. Satisfactory results were achieved in all cases.

## (Miscellaneous)

**The Significance of Pleuropneumonia-like or " L " Organisms in Non-gonococcal Urethritis, Reiter's Disease, and Abacterial Pyuria.** HARKNESS, A. H., and HENDERSON-BEGG, A. (1948). *Brit. J. vener. Dis.*, **24**, 50.

A search for " L " organisms was made by smear and culture methods in 206 male cases of simple non-gonococcal urethritis, of which 132 were of abacterial type, and in 47 cases in which the urethritis was complicated by arthritis. Similar examinations were made on 157 cases of gonorrhoea and on 65 normal persons. Primary abacterial urethritis (Waelsch type) was diagnosed in 57 male patients. " L " organisms were cultured in 21 cases (38%). In one instance of Waelsch urethritis, positive for " L " organisms, which had been contracted by sodomy, these organisms were recovered from the anal canal of the contact. " L " organisms were also recovered in 5 out of 10 cases of acute abacterial urethritis simulating gonorrhoea. In residual abacterial urethritis after successful penicillin therapy for gonorrhoea, of which there were 35 cases in the series, " L " organisms were found in 1 only. The series of 47 cases of urethritis associated with polyarthritis contained 41 in which the urethritis was of abacterial type and of which 7 were positive for " L " organisms. Seven of the cases with polyarthritis presented all the characters of the Reiter syndrome. The authors found " L " organisms in the urethral washings of 2 of the patients but their attempts to recover the organism from synovial fluid, conjunctival secretion, and skin lesions were not successful. [" L " organisms in the joint fluid in a case of Reiter's syndrome have since been reported by Warthin (*Amer. J. Med.*, 1948, **4**, 827), and Dienes and his colleagues report

finding the organisms in the synovial fluid of 2 similar cases (*New Engl. J. Med.*, 1948, **238**, 509).

Non-gonococcal cervicitis and vaginitis in women was also investigated, " L " organisms being recovered in 12 of 46 cases. They were also found in 3 of 18 women with acute gonorrhoea. Attempts to find the organisms in normal persons—59 men and 15 women—were unsuccessful.

Serological investigations—agglutination and complete fixation—were carried out on suitable cases at various stages of the disease but these were negative. None of the strains isolated was pathogenic to white mice, rabbits, or guinea-pigs. *V. E. Lloyd.*

**Arthritis, Conjunctivitis, and Urethritis (So-called Reiter's Syndrome) in a Four-year-old Boy.** FLORMAN, A. L., and GOLDSTEIN, H. M. (1948). *J. Pediat.*, **33**, 172.

A 4-year-old white male child was admitted to hospital suffering from a bilateral oedematous purulent conjunctivitis of 2 days' duration and pain in the right knee, which had been swollen for 1 day. The illness had started a week before admission with diarrhoea without blood or mucus in the stool. Two days previously urgency of micturition, frequency, and dysuria were also present. The child was acutely ill with a rectal temperature of 102° F. (38·9° C.). There was a leucocytosis of 20,050 per c.mm. (79% polymorphonuclears) and the erythrocyte sedimentation rate was 120 mm. in one hour.

The only organism recovered from the conjunctiva was *Staphylococcus albus* and from the knee a chromogenic bacillus—neither being considered significant. Nothing was obtained from prostatic culture and only *Bacterium coli communis* from the stool. Blood cultures were likewise negative. The corneae of 2 rabbits were sacrificed and the urethral exudate was applied ; the fluid from the knee-joint was also injected intracerebrally and intraperitoneally into 5 Swiss mice—all without effect. The gonococcal complement-fixation reaction was negative, as were agglutination reactions to a pleuropneumonia-like organism obtained from a case of subacute bacterial endocarditis. Agglutination reactions were also negative to *Salmonella*, *Brucella*, and *Proteus OX* 19. Antibodies in high titre were, however, found for *Shigella flexneri VII* and *VIII*, though there was a gradual decline in the agglutinin titre from 1 in 1,280 to 1 in 40 during the 6 weeks that the patient was in hospital.

[A case of keratosis blennorrhagica in a child of 7 was recently reported by Gault and Gault (*Indian med. Gaz.*, 1948, **83**, 123).] *R. R. Willcox.*

**Reiter's Disease : Report of Five Cases Including Two Successfully Treated with Hyperthermia.** LOWMAN, E. W., and BOUCEK, R. J. (1948). *Ann. intern. Med.*, **28**, 1075.

Five cases of Reiter's disease, all in white males 22 to 26 years old, are described. Two cases were treated by hyperthermy, which has been acknowledged in Britain for some years to be the best treatment for Reiter's disease.

**Reiter's Syndrome. A Report on Four Patients Treated with Streptomycin.** WARTHIN, T. A. (1948). *Amer. J. Med.*, **4**, 827.

Four male patients with Reiter's disease were treated with streptomycin. As the disease is one in which regression may occur at any time, and as some of the cases treated were already of long duration, even although the results are distinctly encouraging the possibility of coincidence is not overlooked and the conclusions are cautious.

**Palindromic Rheumatism—Effective Treatment with Gold.** GINSBURG, M. (1948). *Ohio St. med. J.*, **44**, 707.

A white male suffering from palindromic rheumatism was between June and October, 1947, given 440 mg. solganal B intramuscularly, in doses of from 10 mg. to 40 mg. at gradually increasing intervals of from one week to two weeks, with considerable relief.

**Rheumatism in the Aged.** ISHMAEL, W. K. (1948). *Geriatrics*, **3**, 217.

The manifestations and treatment of the various forms of arthritis in the aged are considered, particularly the shoulder-hand syndrome and osteo-arthritis of the hip. The causes of bone atrophy are reviewed and suggestions made concerning treatment. The author concludes that the management of these patients depends on accurate diagnosis, after which treatment is usually obvious and effective. *T. G. Reah.*

**Social and Nutritional Factors in Adolescent Osteochondritis of the Spine.** KEMP, F. H., WILSON, D. C., and EMRYS-ROBERTS, E. (1948). *Brit. J. soc. Med.*, **2**, 66.

This paper summarizes a series of investigations conducted on the distribution and the hitherto obscure aetiology of juvenile osteochondritis of the spine (Scheuermann's disease), and gives an account of its relation with malnutrition and a possible relation with fluorine. It is thought that in view of the known association of endemic dental and osseous fluorosis with malnutrition in other countries, the possibility of a similar association in the case of dental fluorosis and juvenile osteochondritis in Britain should be borne in mind.

**Treatment of Pathological Dislocation of the Hip Joint after Suppurative Arthritis in Infants.** BRYSON, A. F. (1948). *J. Bone Jt Surg.*, **30B**, 449.

Seventeen cases of pathological dislocation of the hip-joint following suppurative arthritis in the first year of life are reviewed.

**Radiological Features of the Sella Turcica in Chronic Rheumatism.** (Aspects radiologiques de la selle turcique dans les affections rhumatismales chroniques.) LEHMANN, P., LEDINH-THI, —., and BELLIN, —. (1948). *Bull. Soc. méd. Hôp. Paris*, **4**, 666.

A preliminary study of 72 skulls revealed that the site of the sella turcica varied, being usually 6 to 26 mm. above the nasion-inion plane. In the series of 161 cases, the size of the sella was classified as either normal or small, the latter type being present in 78 out of 97 cases of chronic rheumatism, 11 out of 23 cases of post-traumatic rheumatism, 5 out of 11 patients with congenital spinal deformities, and 11 out of 30 with other diseases. The interclinoid distance was less than 2 mm. in 58 of the cases with chronic rheumatism, being completely closed by a bony bridge in 11, of whom 2 had genital hypoplasia. The sella was also bridged in 2 patients with congenital deformities and in 1 " non-rheumatic ". More than half the patients with rheumatism had widened anterior and posterior clinoid processes with decalcification, most often in the posterior

processes. This was less obvious in the non-rheumatic diseases, even after allowing for age. [The age limits of the various groups are not given.] The authors conclude that persons with this small type of sella, which is often closed and has widened clinoid processes, are predisposed to rheumatic diseases.

[The criteria for assessing the size of the sella turcica are not given, and the number of controls studied is too small for the comparison to be convincing.] *I. Ansell.*

**Anatomical Studies on Lumbar Disc Degeneration.** [In English.] FRIBERG, S. (1948). *Acta orthopaed. scand.*, **17**, 224.

Observations on intervertebral disk degeneration are recorded. The author is convinced that almost every disk prolapse is preceded by degeneration, and that trauma only plays the part of a liberating factor. He advises caution as regards explorative laminectomy, and recommends greater use of lumbo-sacral fusion.

## Sciatica

**Vegetative Hypertrophic and Atrophic Sciatica.** (La névralgie sciatique végétative hypertrophique et atrophique.) PITHA, V. (1947). *Rev. neurol.*, **79**, 491.

The author seeks to isolate from the general group of "sciaticas" a new syndrome in which sciatic pain is associated with muscular hypertrophy and hypertonus on the one hand and with atony and wasting on the other. In each case the tendon reflexes are alleged to remain unaltered. The author believes that this special syndrome may be observed in cases resulting from a displaced intervertebral disk as well as in cases of neuritic origin. *J. St. C. Elkington.*

**The Removal of Lower Lumbar Intervertebral Discs by the Transabdominal Extraperitoneal Route: A Preliminary Report of Three Cases.** HARMON, P. H. (1948). *Permanente Fdn med. Bull.*, **6**, 169.

The author's thesis is that incomplete removal is responsible for recurrent symptoms after disk operations, and that late paraesthesiae are caused by nerve root retraction. These can be avoided if an abdominal approach is used which allows near-total excision and is completed by fusion of the vertebral bodies. With an extraperitoneal exposure similar to that used for lumbar sympathectomy, the fifth lumbar disk can be attacked from in front and the fourth disk from the antero-lateral aspect. After removal of the disk, iliac bone is packed in between the "rawed" vertebral bodies. Patients are allowed up on the second or third day in a spinal brace.

[It is doubtful whether surgeons who have mastered the exacting technique of laminectomy will be inclined to abandon it for an approach through a relatively unfamiliar field. Admittedly, there is less local bleeding, but it is impossible to deal with any coincident lesion within the spinal canal. Moreover, as in the abdominal operation of spondylolisthesis the risks to the great vessels and the danger of postoperative retroperitoneal haemorrhage and mesenteric thrombosis will discourage imitation.] *David Le Vay.*

**Experimental Intervertebral-disc Lesions.** KEY, J. A., and FORD, L. T. (1948). *J. Bone Jt Surg.*, **30A**, 621.

Postoperative failures in intervertebral disk surgery in the authors' hands amounted to between 5 and 10% of cases. Secondary operation failed to reveal the cause of this. Experimental work was therefore carried out on dogs. Bony ankylosis was never produced after curettage; protrusion was more pronounced in disks which were incised than in those which were curetted; a protrusion followed in only 1 of the disks which were punctured; postoperative adhesions to nerve roots were of impressive extent, and these might be responsible for postoperative symptoms. *J. G. Bonnin.*

**Diagnostic Puncture of Intervertebral Disks in Sciatica.** [In English.] LINDBLOM, K. (1948). *Acta orthopaed. scand.*, **17**, 231.

The injection of contrast medium by needle puncture into the centre of intervertebral disks to demonstrate herniation radiologically is described. Although only a small number of cases has been studied and the interpretation of radiographs may be difficult, on the whole the most exact diagnosis was given by this method and the agreement with the operation findings was complete. It would appear that further study of this method may prove of great value. (For the technique the original should be consulted.) *G. Blundell Jones.*

## Non-articular Rheumatism

**Fibrositis.** CYRIAX, J. (1948). *Brit. med. J.*, **2**, 251.

The author thinks that primary fibrositis, whether local or generalized, is an imaginary disease, the symptoms being due to internal derangements of the spinal joints. The possibility of secondary fibrositis—rheumatoid and traumatic—is admitted.

**B Diethylaminoethyl Dehydrocholate in the Treatment of Fibrositis.** RODEN, D., and WRIGLEY, F. (1948). *Irish J. med. Sci.*, **6**, 330.

B-Diethylaminoethyl dehydrocholate, 5 mg. subcutaneously or intramuscularly was given at intervals of 1 to 3 days to a total of 5 to 20 injections to 100 patients with primary fibrositis; 28 became symptom-free; 28 derived no benefit. Of a further series of 50 cases, 40 became symptom-free. The results are unconvincing but justify the author's plea for further trial.

**The Shoulder-Hand Syndrome.** (Skulder-Haandsyndromet). ØSTER, J. (1948). *Ugesk. Læg.*, **110**, 951.

The shoulder-hand syndrome is discussed, reference being made to 5 cases directly observed, 45 cases in the recent records of the municipal hospital, Aarhus, Denmark, and the literature.

**Ischemic Contracture, Local, in the Hand.** BUNNELL, S., DOHERTY, E. W., and CURTIS, R. M. (1948). *Plast. reconstr. Surg.*, **3**, 424.

The cause of a "fibrous contracture of the intrinsic muscles of the hand similar in pathology to Volkmann's ischemic contracture in the forearm" is decreased circulation such as may follow injury to the brachial plexus or the axillary or brachial arteries, the application of a plaster cast including the hand, or burns. The muscles chiefly affected are the interossei, the lumbricals, and the thenar and hypothenar groups. The deformity is that of acute flexion at the metacarpo-phalangeal joints with extension of the inter-phalangeal joints of all 4 fingers and adduction of the thumb into the palm with extension at the interphalangeal joint.

Treatment consists in stripping the interossei from their attachments to the shafts of the metacarpals through two incisions placed on the dorsum of the hand. Actual

division of the tendons of the interossei and lumbricals at their points of attachment to the dorsal expansion may be necessary, particularly when all elasticity in the muscle bellies has been lost. The thumb is dealt with through a dorsal incision through which all fibrous tissue in the muscles is excised ; if the adductors are active but too short, the adducted position of the thumb is relieved by detaching their origin from the third metacarpal. Capsulectomy of the carpo-metacarpal joint of the thumb may also be necessary. By these measures the position of the hand and its function can be improved.

[This clinical entity has often been noted but no clear description of its pathology and treatment has previously been advanced ; this paper represents a further important step in the treatment of disabled hands.]

*Rainsford Mowlem.*

## General Pathological Articles

**Pathological and Anatomical Study of a Case of " Cured " Milkman's Syndrome.** (Pathologischanatomische Untersuchungen bei einem Fall von " geheiltem " Milkman-syndrom.) KIND, A. (1947). *Schweiz. Z. Path. Bakt.*, **10**, 143.

An undernourished 79-year-old single woman with Milkman's syndrome complained of severe pains in her bones; her entire skeleton was tender on pressure, and her ribs soft. *X*-ray examination revealed generalized diffuse osteoporosis, pseudo-fractures of the os pubis and ulnae, fractures of the ribs, and heart-shaped deformity of the pelvis. There was early formation of uncalcified callus round the pseudo-fractures of the os pubis. Calcium and phosphorus levels in blood were normal, but the [alkaline] phosphatase was increased. No disturbance of calcium balance was found. A biopsy specimen taken from the iliac crest showed changes typical of senile osteomalacia. The skeletal pains disappeared after treatment with large doses of calcium phosphate and vitamin D, but there was only slow improvement in the calcification of bones. In an accidental fall, about 9 months after admission to hospital, the patient fractured her right femur; the fracture healed with good callus formation in 3 months. Fifteen months after admission the patient was regarded as cured, but after an attack of asthma she died with cardiac failure. Necropsy revealed cardiac hypertrophy and dilatation of both ventricles, atherosclerosis of coronary and other arteries, arteriolosclerotic contraction of kidneys, pulmonary oedema, and emphysema. Histological examination of the bones disclosed extensive osteonecrotic changes and microscopical fissures. It is concluded that Milkman's syndrome is due to aseptic traumatic necrosis of bone tissue.

*G. Popják.*

**Glucuronic Acid Deficiency in the Rheumatic Diseases.** PETERMAN, E. A. (1947). *J. Lancet*, **67**, 451.

Glucuronic acid is produced in the body, possibly in the liver and muscles, as a product of glucose metabolism. The author offers the theory that if focal infection or " toxicity in general " calls for an increase in the amount of glucuronic acid needed for detoxication there will be a resultant deficiency of glucuronic acid not only for detoxication but also for the rebuilding of worn tissues. He describes the work done on dogs and a human volunteer to demonstrate that glucuronic acid, when administered by mouth or by injection, does not give rise to toxic effects. A patient suffering from rheumatoid arthritis was treated with glucuronic acid and " has enjoyed a sustained improvement now for 34 months ". This led the author to treat 52 patients with the calcium, potassium, or sodium salts of glucuronic acid. These patients included sufferers from rheumatoid arthritis, fibrositis, osteo-arthritis, " mixed arthritis ", diabetic neuritis, sciatic neuralgia, haemophilic arthritis and multiple sclerosis, and patients who had not completely recovered after rheumatic fever. In 1 patient with multiple sclerosis and 7 of the others there was no improvement, but the remainder showed " satisfactory response ".

*W. Tegner.*

**Distribution of Gold in the Animal Body in Relation to Arthritis.** BERTRAND, J. J., WAINE, H., and TOBIAS, C. A. (1948). *J. Lab. clin. Med.*, **33**, 1133.

Radioactive gold, $Au^{198}$ (half life, 2·7 days) with a specific gravity of 2·5 mc. per mg. was converted into gold sodium thiosulphate, which was injected intravenously in a series of studies on the distribution of gold in rats, rabbits, and man. Urine, faeces, and tissues were analysed after nitric acid and hydrogen peroxide digestion by a bell jar Geiger-Müller counter with a thin mica window, the gold being previously deposited on planchets by electrolysis.

Urine and faecal excretion becomes slow after the first week, a total of 23% of the 1 mg. administered being excreted in 8 days ; 97·75% was recovered from carcase blood and excreta. Distribution amongst various organs and tissues was studied on 15 rats given 1 mg. of gold containing 1 mc. of radioactivity, and 10 rabbits. They were bled out by saline perfusion before being killed. In both species the order of concentration was approximately the same—kidney (6 to 8% of total dose per g. tissue), spleen (1 to 2%), liver (0·7 to 1%), synovialis (0·23 to 0·67%), and muscle (0·03 to 0·07%). A small amount passes into the eye and brain.

In chemical synovitis and also in myositis produced by two intra-articular turpentine-diethyl-ether (3 : 1) injections of 0·5 ml. with a 5-day interval, the tissue took up a significantly greater amount of gold not accounted for merely by the presence of pus. In a woman with rheumatoid arthritis after 2·5 mg. of gold (1,010 mc.) had been given, a biopsy was performed on an affected knee. Of the tissues taken, by far the greatest concentration of gold was present in the synovialis.

*E. G. L. Bywaters.*

**Study of Humoral Changes in Rheumatic and Joint Conditions. III. The Cadmium Sulphate Flocculation Reaction (Wünderly's Reaction). IV. The Weltmann Reaction.** (Étude des modifications humorales dans les affections rhumatismales et articulaires, III. Étude de la réaction de flocculation au sulfate de cadmium (réaction de Wunderly). IV. Étude de la réaction de Weltmann.) COSTE, F., and DELBARRE, F. (1948). *Bull. Soc. méd. Hôp. Paris*, **4**, 648.

The Wunderly reaction—in which flocculation occurs when 0·2 and 0·25 ml. of 0·4% solution of cadmium sulphate is mixed with 0·4 ml. of serum—was applied to 200 sera. The authors suggest that the reaction can be of value in recognizing quickly those cases of an inflammatory or infective origin which require further investigation.

The authors applied the Weltmann reaction to 400 sera. It is suggested that a negative reaction, which indicates a diminution in the zone of coagulation of serum protein in the presence of calcium chloride, corresponds with an increase in the haptoglobinaemic index of the serum and may be related to an alteration of the $\alpha$-globulin.

*E. T. Ruston.*

**Quantitative Antistreptokinase Studies in Patients Infected with Group A Hemolytic Streptococci: A Comparison with Serum Antistreptolysin and Gamma Globulin Levels with Special Reference to the Occurrence of Rheumatic Fever.** ANDERSON, H. C., KUNKEL, H. G., and MCCARTY, M. (1948). *J. clin. Invest.*, **27**, 425.

The liquefaction of human fibrin clot by streptokinase has been shown to be due to the combined effect of an inactive proteolytic enzyme in the plasma and the active substance obtained from cultures of haemolytic streptococci. The reaction is analogous to the conversion of trypsinogen to trypsin by enterokinase. Further streptokinase produces marked liquefaction of human fibrin clot, whereas it causes only minor changes in clots from other animal species. The first quantitative method for the estimation of antibody directed against streptokinase involved a neutralization test in which a constant standardized amount of streptokinase is incubated with serial dilutions of the serum, following which an indicator system consisting of fibrinogen, plasminogen (the inactive form of the proteolytic enzyme), and thrombin is added. In the present study quantitative antistreptokinase determinations have been carried out on specimens obtained from patients suffering from scarlet fever. The primary aim of the investigation was to determine whether or not significant differences in antibody response existed between patients who developed rheumatic fever after an attack of scarlet fever and those who did not.

Full details are given of the technical methods employed. In general, the authors have found that after infection of patients with group A haemolytic streptococci the antibody for streptokinase develops in the same way as does antistreptolysin O, and that at the same time there is an increase in the serum $\gamma$ globulin. In some of the patients with uncomplicated scarlet fever the rise in antibody titre was greater than in certain of the rheumatic patients, in some of whom there was a relatively insignificant increase. On the average, however, those who developed rheumatic fever as a sequela to a streptococcal infection showed a greater antibody response than those who did not. *J. Smith.*

**Streptococcal Hyaluronic Acid and Hyaluronidase. I. Hyaluronidase Activity of Non-capsulated Group A Streptococci. II. Production and Subsequent Destruction of Hyaluronic Acid by Certain Strains of Group A Streptococci. III. Virulence of Group A Streptococci for Mice in Relation to the Production and Destruction of Hyaluronic Acid.** PIKE, R. N. (1948). *J. infect. Dis.*, **83**, 1.

It has previously been demonstrated that only certain strains of haemolytic streptococci produce hyaluronidase and that the enzyme produced by streptococci differs from that of other bacteria in its sensitivity to *p*H, in adaptive production, in the products of hydrolysis, and in antigenic specificity. The present series of reports deals with its detection, and its production by streptococci.

These observations yield no evidence that mouse virulence is correlated with either the rate of appearance of hyaluronic acid or the rate of its disappearance.
*G. T. L. Archer.*

**Bone and Joint Changes in Hemophilia, with Report of Cases of So-called Hemophilic Pseudotumor.** GHORMLEY, R. K., and CLEGG, R. S. (1948). *J. Bone Jt Surg.*, **30A**, 589.

In a series of 76 patients with haemophilia, 44 showed evidence of pathological changes in the bones or joints. All the patients were males and the average age was 17·3 years. The known age at the onset of haemarthrosis averaged 7½ years. Weight-bearing joints were involved more frequently than non-weight-bearing joints, and the knee about twice as often as any other joint. Single joints were involved in 10, multiple joints in 34.

Unusual bone changes occurred in 6 patients. The femur was involved in 4, the olecranon in 1, and the phalanx of the thumb in 1. The chief clinical feature in these cases was marked swelling of the thumb, producing what the authors describe as a haemophilic pseudotumour. The tumour consisted essentially of a large subperiosteal haematoma. Periosteal new bone formation may occur, and pressure erosion causing absorption and destruction of the underlying bone may lead to a pathological fracture. Pathological fracture followed by secondary infection and haemorrhage from the tumour was responsible for the death of 3 of the 4 patients in whom the femur was involved. *J. S. Batchelor.*

**The Effect of Sodium Bicarbonate on the Renal Excretion of Salicylate.** WILLIAMS, F., and LEONARDS, J. R. (1948). *J. Pharmacol.*, **93**, 401.

The administration of alkali (160 mg. sodium citrate and 25 mg. sodium bicarbonate) to rats receiving sodium salicylate (50 mg. per 100 g. body weight) had no influence upon the gastro-intestinal absorption of the latter drug. In normal female dogs, an oral dose of 0·5 g. of sodium salicylate every 3 hours was well tolerated. Serum salicylate content rose gradually to a level of about 60 mg. per 100 ml. after 2 days. When the blood level was stabilized, the dog received 1·6 g. of sodium citrate and 0·25 g. of sodium bicarbonate in addition to the regular dose of sodium salicylate. The serum salicylate level fell within 3 to 6 hours to a level of about 30 mg. per 100 ml. During the next 2 days the level declined irregularly to a final low value of 15 mg. per 100 ml. When the citrate and bicarbonate administration was stopped the salicylate level began slowly to rise again. The urinary excretion of salicylate showed a significant increase with the administration of bicarbonate, and this increase was of a sufficient size to account for the decreased blood level.

The effect of alkali on the renal clearance of salicylate in 4 human subjects was similar to that observed in the dog. Sodium bicarbonate increased the salicylate clearance but the effect was not as striking as that in the dog, partly because there appeared to be more salicylate bound to the plasma protein in the human subject. The increase in clearance as the *p*H of the urine increased was due mainly to an increase in the excretion of unconjugated salicylate. *G. B. West.*

**Biochemical Studies of Salicylic Acid and a Series of its Derivatives.** MARTIN, G. J., and BYERS, S. (1948). *Amer. J. digest. Dis.*, **15**, 127.

This is a study of the levels of salicylate in rabbit blood after the administration of various salicylate derivatives. The results demonstrate that intravenous saligenin is rapidly oxidized and gives rise to blood levels roughly comparable to those after injection of salicylic acid. The duration of significant blood levels (30 mg. per 100 ml.) is similar. The oxidation does not occur in the blood stream, but presumably in the liver. The administration of mixtures of saligenin and salicylic acid does not materially alter the blood levels obtained. Acetylsalicylaldehyde administration produces a low blood level (5 mg. per 100 ml.), which persists for 8 hours. After salicyoyl-$\beta$-alanide had been given orally (1 g.

and 1·8 g.) no salicylate was found in any blood samples taken up to 22 hours after administration. After nicotinyl salicylate (100 mg. per kilo) had been given orally the blood levels of 4 mg. per 100 ml. were found even after 40 hours. Acetylsaligenin, disalicylic acid ester of succinic acid, and acetylsalicylaldehyde diacetate gave low and poorly maintained salicylic acid levels in the blood. It is suggested that these compounds do not merit further study. *J. Dawson.*

**Observations Concerning the Effects of (1) Sodium Salicylate and (2) Sodium Salicylate and Glycine Upon the Production and Excretion of Uric Acid and Allantoin in the Rat.** FRIEDMAN, M. (1948). *Amer. J. Physiol.*, **152**, 302.

Sodium salicylate was found to effect an immediate increase in the urinary excretion of uric acid of the normal rat without a preceding or concomitant change in the blood uric acid, the renal plasma flow or the glomerular filtration rate. Sodium salicylate was found to exert no effect either upon the blood or urinary allantoin content of the normal rat. Glycine was not found to augment significantly the effect of sodium salicylate in increasing the excretion of uric acid. Sodium salicylate was unable to cause any significant change in the blood uric acid or allantoin of the nephrectomized rat. The chronic administration of sodium salicylate was found to cause an immediate and continued increase in uric acid excretion. The blood uric acid of such treated animals progressively fell to approximately one-third of its control value. It was concluded that salicylate acts to increase the output of uric acid by interfering with the tubular mechanism concerned with the excretion of uric acid.—[Author's conclusions.]

**Clinical Value of Some Methods of Estimating Erythrocyte Sedimentation Rate.** SINTON, J. R. (1948). *Brit. med. J.*, **1**, 391.

A comparison was made between the erythrocyte sedimentation rates (Westergren and Wintrobe techniques) of 61 female patients with pulmonary tuberculosis. The corrections of Wintrobe and of Whitby and Hynes for anaemia were applied. It was found that the Westergren method gave figures that " agreed better " with the clinical course than did those obtained by either of the methods involving correction. It is concluded that this is the most useful method in assessing the degree of activity of the disease and the direction of its progress.

**Value of Mester's Reaction and its Modifications in the Diagnosis of Rheumatism.** (Valor de la reaccion de Mester y sus modificaciones en el diagnostico de la enfermedad reumatica.) SERRATE, J. P., and ORFIA, A. B. (1948). *Rev. esp. Pediat.*, **4**, 32.

Modifications of Mester's technique are described, and details are given of 4 short series of cases so tested. The authors think that the test may be of value in cases of carditis of doubtful origin.

**Study of the Collodion Reaction in Rheumatism.** (Étude de la réaction du collodion dans les affections rhumatismales.) COSTE, F., DELBARRE, F., and LÉVY-MARCHAL, C. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 521.

An attempt was made to confirm the observation of Wallis that certain sera in rheumatoid arthritis have the power of flocculating a colloidal suspension of collodion. No correlation was found between collodion flocculation and streptococcal agglutination. It is not a specific reaction for any disease or disease group, and is of no diagnostic value. The reaction may be positive in many disease processes.

**Further Studies on the Weltmann Serum Coagulation Reaction.** SIEGEL, L. H., and KRAEMER, M. (1948). *J. Lab. clin. Med.*, **33**, 618.

Kraemer has continued his investigations (*Amer. J. digest. Dis.*, 1942, **9**, 129) with the simple Weltmann test, and has applied it to more than 3,000 patients, mainly with gastro-intestinal symptoms. He has reduced the number of tubes from 10 to 6, and has confirmed that a shift to the left indicates an exudative or inflammatory lesion, whilst a shift to the right is associated with fibrosis. A sudden change in the Weltmann reaction accompanied the development of a pleural effusion due to metastatic carcinoma. A positive result is considered of more diagnostic value than an increase in the erythrocyte sedimentation rate. *E. T. Ruston.*

**The Thymol Turbidity Test in Various Diseases.** STILLERMAN, H. B. (1948). *J. Lab. clin. Med.*, **33**, 565.

The author reports a series of thymol turbidity tests carried out on 567 persons. The test is of value in recording the progress of infective hepatitis, and supplies suggestive evidence of liver damage in rheumatoid arthritis.

**Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients with Rheumatoid Arthritis.** ROSE, H. M., RAGAN, C., PEARCE, E., and LIPMAN, M. O. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 1.

An agglutination test is described which is specific for active rheumatoid arthritis. For the technique the original paper should be consulted.

## Other General Articles

**Citrin and Ascorbic Acid Therapy in Chronic Arthritis and Toxaemia of Pregnancy.** (Citrin- och askorbinsyratillforsel vid kronisk polyartrit eller graviditetstoxikos.) EKMAN, B. (1948). *Nord. Med.*, **38**, 1112.

The author followed up earlier observations on the detoxicating action of flavones by administering citrin in cases of chronic polyarthritis with a raised indole excretion. A daily dose corresponding to 45 mg. of quercetin was given intravenously to 10 patients for 10 days, during which time the average daily indole excretion fell by about 50% and the average daily indoxyl sulphate excretion by about 25%. Similar results were obtained in a subsequent series. Large doses of ascorbic acid had no effect on indole excretion. No clinical change was produced in the rheumatic condition of any of the patients. Citrin and ascorbic acid were then administered to 10 patients with toxaemia of pregnancy; the daily dose of the former corresponded to 150 mg. of quercetin, and the daily dose of the latter was 300 mg. There was an immediate fall in blood pressure and in albuminuria as measured by the Esbach method. Only 3 patients remained in hospital long enough for the effect of withdrawal to be observed, and in all these the cessation of therapy was followed by a rise in blood pressure and return of albuminuria; these signs responded well to renewed administration. *B. Nordin.*

**Changes in the Bacterial Flora of the Throat and Intestinal Tract During Prolonged Oral Administration of Penicillin.** LIPMAN, M. O., COSS, J. A., and BOOTS, R. H. (1948). *Amer. J. Med.*, **4**, 702.

The authors record their observations on changes in the normal bacterial flora of throat and intestinal tract during and after oral administration of amorphous penicillin (sodium salt). (*a*) Bacterial flora of the throat consisting of predominantly Gram-positive cocci before treatment became predominantly Gram-negative during treatment, and cessation of therapy produced rapid reappearance of Gram-positive organisms. Gram-negative coliform bacillus were observed during treatment only. (*b*) Bacterial flora of the intestinal tract showed no significant change in the character of the organisms. The only change observed was a lower incidence of streptococcus-positive stool cultures during treatment, compared with periods before or after penicillin therapy. The authors also studied the penicillin-sensitivity of these organisms ; there was no evidence to show that bacterial resistance to penicillin developed during the prolonged therapy. *S. Karani.*

**Bronchial Carcinoma Presenting as Polyneuritis.** WYBURN-MASON, R. (1948). *Lancet*, **1**, 203.

Three cases are described in men, aged 52, 59, and 71 years in whom the presenting symptoms were those of peripheral neuritis, but who, at necropsy, were found to have had bronchial carcinoma. There was no evidence of involvement of the nerves or ganglia or of secondary deposits in the cord, brain, or vertebrae. The author discards the theory of a " toxic " or " metabolic " action on the peripheral nerves from the carcinoma, and suggests a disturbance of nervous function produced reflexly from the lungs. He quotes the analogy in certain lung diseases of hyperthrophic pulmonary arthropathy which may disappear after removal of the diseased lung or after ligation of the pulmonary artery supplying the segment of lung affected. In the 3 cases quoted the bronchial carcinoma was advanced, and in the third case there was also carcinoma of the stomach. [The evidence in favour of the " lung reflex " theory is not convincing; there is no note of the presence of finger-clubbing in the case.] The author stresses the importance of searching for a primary tumour in elderly patients with polyneuritis when the general condition is deteriorating.
*J. L. Livingstone.*

## Titles of other Articles in the Current Literature

**Rheumatic Fever in Relation to Other Fevers of Allergic Origin.** (La fièvre rhumatismale dans ses rapports avec les autres fièvres de nature allergique.) GIRAUD, P., BERNARD, R., and ROUSSET, —. (1948). *Sem. Hôp. Paris*, **24**, 1626.

**Acute Rheumatism of the Lung.** (Reumatismo pulmonar agudo.) BIANCHI, A. E., and TOBIAS, J. W. (1947). *Arch. Soc. argent. Anat. norm. patol.*, **9**, 99.

**Skin Manifestations of Rheumatic Fever.** GRIFFITH, G. C., and CAMPBELL, A. D. (1948). *Amer. Practit., Phila.*, **2**, 622.

**Initial Symptoms in Rheumatic Fever.** (Initialsymtomen vid reumatisk feber.) JACOBSSON, E. (1948). *Nord. Med.*, **39**, 1319.

**Chronic Progressive Inflammatory Rheumatism with Valvular Heart Lesions.** (Rhumatisme chronique progressif inflammatoire avec cardiopathie valvulaire.) WEISSENBACH, R.-J., FAULONG, L., and GACON, R. (1948). *Rev. Rhum.*, **15**, 234.

**Incidence of Sickle Cell Anemia with Rheumatic Heart Disease.** OHRENSTEIN, I. R. (1948). *J. Pediat.*, **33**, 186.

**A Therapeutic Regimen for Acute Rheumatic Heart Disease in Children.** TARAN, L. M. (1948). *J. Pediat.*, **33**, 226.

**Acute Rheumatism and Streptococci.** (Rhumatisme articulaire aigu et streptocoque.) ANDRIEU, G., MONNIER, J., and CARRIERE, M. (1948). *Paris méd.*, **28**, 341.

**Streptococcal Infection and Acute Rheumatism.** (Infection streptococcique et rhumatisme articulaire aigu.) RUDOLF, M. (1948). *Pr. méd.*, **56**, 494.

**Joint Deformities and Indolent Skin Ulceration Following Acute Rheumatism.** (Déformations articulaires et ulcération cutanée torpide consécutives à un rhumatisme articulaire aigu.) WORMS, R., and TUBIANA, M. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 602.

**Rheumatic Pneumonia.** [In English.] VAN WIJK, E. (1948). *Acta paediatr., Stockh.*, **35**, 108.

**The Rheumatic Fever Community Program. Its Value in the Epidemiological Study of Rheumatic Fever. Summary of the Symposium Prepared by the Moderator.** RUTSTEIN, D. D. (1948). *Amer. J. publ. Hlth.*, **38**, 1082.

**Rheumatic Fever.** HANSEN, A. E. (1948). *Tex. Rep. Biol. Med.*, **6**, 150.

**Newer Concepts of Rheumatic Fever.** GRIFFITH, G. C. (1948). *Ann. w. Med. Surg.*, **2**, 325.

**Mono-articular and Extra-articular Forms of Acute Rheumatism.** (Formas mono y extra-articulares de la enfermedad de bouillaud.) BERETERVIDE, E. A. (1948). *Rev. Med. Cienc. af.*, **10**, 323.

**Two Atypical Cases of Acute Rheumatism.** (Sur deux cas atypiques de maladie de Bouillaud.) LEMIERRE, A., and MORIN, M. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 837.

**The Mechanism of Hypertension in Acute Rheumatic Fever.** HARRIS, C. M. (1948). *J. Bowman Gray Sch. Med.*, **6**, 101.

**A Case of Rheumatic Carditis Treated Successively with Sodium Salicylate and Penicillin in a North African Moslem.** (Sur un cas de rhumatisme cardiaque traité successivement par le salicylate de soude et la pénicilline chez un musulman nord-africain.) RAYNAUD, R., and CLAUDE, R. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 791.

**Recurrent Laryngeal Nerve Palsy and Cardiac Lesions. The Role of Rheumatic Mediastinitis.** (Paralysie récurrentielle et cardiopathie. Le rôle de la médiastinite rhumatismale.) LUTEMBACHER, R. (1948). *Rev. argent. Reum.*, **13**, 90.

**Scapulo-humeral Periarthritis.** (La périarthrite scapulo-humérale.) BILLE, A. (1948). *Acta physiother. rheum. belg.*, **3**, 90.

**Radiological Features of the Calcifications and *X*-Ray Therapy in Scapulo-Humeral Periarthritis.** (Aspetto radiologico delle calcificazioni e roentgenterapia nella periartrite scapolo-omerale.) RAFFAELLI, M. (1947). *Radiologia, Roma*, **3**, 295.

**Gold Treatment of Rheumatism.** (Die Goldbehandlung des chronischen Gelenkrheumatismus.) WINKLER, W. (1948). *Therap. Umsch.*, **5**, 43.

**Antireticular Cytotoxic Serum in the Treatment of Arthritis. Observation on Forty-four Cases.** SOLOMON, W. M., and STECHER, R. M. (1948). *J. Lab. clin. Med.*, **33**, 768.

**Takata Reaction in Rheumatoid Arthritis.** (A Tatkaa-reactio viselkedése rheumatoid arthritisnél.) KOVÁCS, L. (1948). *Orv. Lapja*, **4**, 1162.

**Amyloid Disease and Rheumatoid Arthritis.** HILL, L. C. (1948). *Proc. R. Soc. Med.*, **41**, 607.

**Antistreptolysin Titer and Sedimentation Rate in Polyarthritis and Endocarditis in Childhood.** [In English.] THELIN, R. (1948). *Acta paediatr., Stockh.*, **35**, Suppl. 1, 100.

**Use of Sex Hormones in Chronic Rheumatism.** (L'emploi des hormones sexuelles dans les affections rhumatismales chroniques.) COSTE, F. (1948). *Progr. méd., Paris*, **76**, 364.

**The Problem of Chronic Degenerative Rheumatism.** (Le problème du rhumatisme chronique dégénératif.) LERICHE, R. (1948). *Progr. méd., Paris*, **76**, 363.

**Multiple Myeloma Simulating Chronic Progressive Inflammatory Rheumatism.** (Myélome multiple ayant pris le masque d'un rhumatisme chronique progressif inflammatoire.) WEISSENBACH, R.-J., and FAULONG, L. (1948). *Rev. Rhum.*, **15**, 189.

**Pathogenesis of Rheumatism.** (Etiopatogenia de la enfermedad reumática.) ARASA BARNAUR, F. (1948). *Clín. y Lab.*, **45**, 424.

**Value of Mester's Reaction and its Modifications in the Diagnosis of Rheumatism.** (Valor de la reaccion de Mester y sus modificaciones en el diagnostico de la enfermedad reumatica.) PUIG SERRA TE, J., and BARBER ORFIA, A. (1948). *Rev. esp. Pediat.*, **4**, 32.

**Mester's Reaction in Rheumatic Infection.** (La reazione di Mester nell'infezione reumatica.) LIPPI, M. (1948). *Rass. med. Sarda*, **50**, 9.

**Metabolism of Glucides in Acute Rheumatism.** (Le métabolisme des glucides dans le maladie de Bouillaud.) LUTEMBACHER, R., and GALIMARD, J. E. (1948). *Rev. argent. Reum.*, **13**, 9.

**Laboratory Aids in the Diagnosis of Rheumatism.** COLLINS, D. H. (1948). *Practitioner*, **161**, 180.

**Change in the Erythrocyte Sedimentation Rate of Rheumatic Patients Following Therapeutic Bath.** (A vörös vérsejt-süllyédes valtozása rheumás betegeknél a fürdökezelés hátasara.) KOVÁCS, L. (1948). *Orv. Lapja*, **4**, 151.

**Sodium Salicylate Intoxication.** (Intoxicación por salicilato de sodio.) STEINBERG, I. R., and MENGONI, H. R. (1948). *Rev. argent. Reum.*, **13**, 3.

**Fibrositis.** [In English.] ARANA-SOTO, S. (1948). *Bol. Asoc. méd. P. Rico*, **11**, 139.

**The Psychosomatic Aspect of Rheumatism.** [In English.] KATZENELBOGEN, S. (1948). *Bol. Asoc. méd. P. Rico*, **40**, 190.

**The Problem of Psychogenesis in Non-articular Rheumatism.** KENNEDY, A. F. (1948). *Rheumatism*, **4**, 204.

**Does a Pure Muscular Rheumatism Exist ?** (Existe-t-il rhumatisme musculaire pur ?) KAHLMETER, G. (1947). *Acta psychiat., Kbh.*, Suppl. 46, 156.

**A Study of Thymectomy with Parathyroidectomy in Ankylosing Polyarthritis.** (De la thymectomie avec parathyroïdectomie dans la polyarthrite ankylosante.) LERICHE, R. (1948). *Pr. méd.*, **56**, 437.

**Rheumatoid Arthritis : Clinical Features and Some of the Current Concepts in Treatment.** BOLAND, E. W., and HEADLEY, N. E. (1948). *Ann. w. Med. Surg.*, **2**, 289.

**Aortic Regurgitation of Insidious Subacute or Chronic Development in Rheumatism of Childhood.** (La insuficiencia aórtica de evolución solapada subaguda o crónica en la enfermedad reumática del niño.) CORREA, B. D. (1947). *Bol. Liga urug. Reum.*, **2**, 105.

**Palindromic Rheumatism.** GRYBOSKI, J. S. (1948). *Bull. U.S. Army med. Dept.*, **8**, 550.

**Spondylitis Ankylopoietica.** (Spondylarthritis anchylopetica.) IVERSEN, P. F. (1948). *Nord. Med.*, **39**, 1707.

**A Case of Spondylitis Due to Typhoid Fever.** (A propos d'une observation de spondylite eberthienne.) GODLEWSKI, S. (1948). *Rev. Rhum.*, **15**, 195.

**Marie-Strumpell Arthritis and the Undiagnosed Low Back Pain.** BAKER, L. D. (1948). *Neb. St. med. J.*, **33**, 331.

**Sciatica.** (Isjias.) YTREHUS, O. (1948). *Tidsskr. norske Laegeforen.*, **68**, 368.

**Treatment of Lumbago, Sciatica, and Other Painful Vertebral Syndromes by Manipulation.** (Traitement des lumbagos, lumbosciatiques et autres syndromes vertébraux douloureux par les manipulations.) COSTE, F., and GALMICHE, P. (1948). *Bull. Soc. méd. Hôp. Paris*, **4**, 657.

**Surgical Treatment of Lumbago and Sciatica.** (A propos du traitement chirurgical de la lombo-sciatique.) D'AUBIGNÉ, M. (1948). *Rev. Rhum.*, **15**, 193.

# EMPIRE RHEUMATISM COUNCIL

## TWELFTH ANNUAL REPORT

H.R.H. The Duke of Gloucester, President of the Empire Rheumatism Council, presided at the Annual General Meeting held in the State Rooms, St. James's Palace, London, on Tuesday, November 2, 1948.

## DUKE OF GLOUCESTER'S OPENING ADDRESS

I am very glad to be able to preside at this twelfth Annual General Meeting of the Rheumatism Council. It is, I think, generally known that the Council was formed in 1936 to investigate methodically every factor in the causation and treatment of the rheumatic diseases, and the programme of work which has been achieved to date gives us not only satisfaction with past results but inspiration to press vigorously forward with the tasks that lie ahead.

My first duty to-day is to pay tribute to our Chairman, Lord Horder, who apart from being the inspiring influence which brought about the inauguration of the Council has since then, with constant interest and singleness of purpose, afforded it the great benefit of his knowledge and experience. Then to the Members of the Council, to the Executive, and to the Scientific Advisory Committee, I must express my thanks for the able and devoted services they have so freely rendered in a voluntary capacity and which, I am sure, cannot have been given without personal cost and inconvenience.

The Council is at all times happy to place its knowledge and experience at the disposal of all interested bodies and persons, and its comparatively short history reveals a remarkable effort for the benefit of rheumatic sufferers.

The schemes of research begun and envisaged in 1936 were seriously hampered and interrupted by the outbreak of war in 1939, but, in spite of the many difficulties and frustrations due to seven years of world upheaval, it is encouraging to know that the Council found it possible to make substantial grants to many organizations and individuals. I have particularly in mind the financial grants made to the Council's Research Laboratory, and the Rheumatic Department at the Hospital of St. John and St. Elizabeth ; to the Naval Research Foundation ; for Gold Therapy Investigation ; for Travelling Scholarships ; and to many individual research workers.

During my absence in Australia as Governor-General, I was pleased to be kept continually informed of the Council's activities and glad to learn that liberal financial provision has lately been made for a full-scale investigation into the causes of rheumatoid arthritis. Such an undertaking has never before been attempted on so large a scale and in such detail, and the Council obviously felt that this particular disease is urgent, as being the most crippling of all forms of rheumatism. The Council has also given special attention to the all-important question of continuing-education for the benefit of general practitioners and post-graduates.

Evidence of the interest shown in the Council's work is instanced by the numerous requests for guidance, advice and literature about our activities from many countries, while recently applications are being submitted for affiliation, as autonomous Branches of the Council, from the Royal Australasian College of Physicians and from the Dominion of New Zealand. A similar application for affiliation has just been received from the Canadian Rheumatism and Arthritis Society, which has the support of the Ministry of National Health and the Medical Association of Canada, and I am sure you would wish this application to be accepted. These are important steps in the development of the world-wide desires to join in the fight against rheumatism.

It may be said that the rheumatic diseases have been, in the past, the most neglected of all human afflictions in the field of research ; yet none perhaps are more deserving of attention in view of their widespread prevalence. In industry alone it is estimated that three million weeks of work are lost each year by the insured population through rheumatic disease, and that the annual cost of industrial rheumatism is in the neighbourhood of over forty million pounds. This is a serious matter in these days of demand for increased production, and one to which I would direct the attention of all captains of industry and employers of labour in the hope that they will support, with all means in their power, the research activities of the Empire Rheumatism Council.

It is also to the individual that the work of the Council must commend itself. The alleviation of human suffering is something more than a practical expression of pity : every right-minded person should assist the Council to find the answer to the grave problem of rheumatic disease, and only exhaustive and expert research can achieve this end. But on the value of research both to organized

labour and to the individual we shall shortly hear from Dr. Copeman, the Honorary Medical Secretary.

The answer to the rheumatic problem will bring relief from pain and disablement to hundreds of thousands of our fellow-citizens and to millions yet unborn, and it is because we realize the magnitude and vital import of the task that the Council is strengthening its position by applying to become an Incorporated Body.

The full scope of the measures which the Council has in view are costly, and it is to enable them to proceed vigorously with their programme that Lord Horder has issued an appeal for a Rheumatism Research Fund. I greatly hope that this will be successful so that the Council may face the future confident that financial difficulties will not impede its work. The intention of the Council is quite simple ; to conduct an all-out scientific attack upon rheumatism and to support our scientists and research workers in their determined attempt to find the answer to the rheumatism problem. Any real progress in this direction will add fresh laurels to British medical achievement, and, as President, I wish the Council continued success in the important contribution its work is making to the benefit of mankind. HENRY

## ADDRESS BY THE CHAIRMAN OF THE COUNCIL

THE RT. HON. THE LORD HORDER

May it please your Royal Highness. In our agenda to-day you, Sir, have disallowed any item which would have given me an opportunity of moving a vote of thanks to you for so graciously coming to preside here to-day. In doing this you once more show us that you associate yourself personally with our activities, and that that association is not entirely formal. All the same, I am sure that my colleagues on the Council and those who support us would wish me to reaffirm the gratitude we feel towards you for the interest that you continue to take. I do not forget that, as you yourself have mentioned, in the midst of affairs of State away in the Antipodes, in that great Dominion where you represented in such distinguished fashion our King and our country, you were not satisfied with merely reading the Reports of our work but you did personally on more than one occasion enquire concerning them and what was their nature, and the stimulus was of great value to us at that time. (Applause.)

Sir, the Empire Rheumatism Campaign is one of the major pre-occupations of my life, and so I would like personally to say how glad I have been to be associated with you since its inception twelve years ago. I suppose I am really too near this particular crusade in medicine to say whether the Empire Rheumatism Council has justified its birth and its twelve years of life. Its three purposes were very clearly stated when it started, and I think I am correct in saying that the Council has been loyal to its purposes. The first of these was to organize research into the cause (causes, not cause) of rheumatic disease ; the second was to encourage education in respect of rheumatic disease, both medical and lay ; and the third was to stimulate public authorities to provide treatment for rheumatic sufferers at as early a stage in the disease as possible.

Remembering as I do the very considerable advance that has been made during the existence of the Council in all three of those fields I do not think I am claiming too much in saying that in all of them the influence of the Council has not been a minor one. Anyway, we do feel that in the Empire Rheumatism Council there exists a medium through which the public can express its interest in a group of painful and disabling diseases to the national importance of which you, Sir, have referred. Through the work of the Council the public can confidently hope for the utmost that science can give in regard to them, and can look forward to a time when the accumulation of knowledge (slow and painful as it may be to arrive at) will help to relieve both the nation and the individual patient.

Therefore, believing in the Council as I do, I must necessarily continue to support it to the utmost of my ability. We have a long way to go yet, a long way to go in research, because Nature guards her secrets of causation very jealously, it does not part with them easily. As for education, that also is a long term affair. With regard to Governments and public authorities, we sometimes complain that they show a lamentable degree of inertia in medical matters, and sometimes we complain that instead of inertia they adopt an attitude of precipitancy which makes the very foundations of our art and our science rock and threaten to collapse !

The Empire Rheumatism Council, I hope, will stand between the two extremes of inertia and precipitate action. It depends officially, your Royal Highness, upon public support, as does every effort in this country of ours. I agree with the comment which Sir George Elliston has just made, that the things that are done best in Britain are the things that begin with voluntary effort and are carried on by voluntary effort.

I should like to end on the note on which I began, Sir, of thanking you for presiding over us once more. (Applause.)

## RHEUMATISM—THE VALUE OF RESEARCH

W. S. C. COPEMAN

(*Hon. Medical Secretary of the Council*)

Your Royal Highness, my Lords, Ladies and Gentlemen,—We are exhorted by the writer of the Book of Ecclesiasticus to honour the physician for he searcheth out the causes of diseases. This will do, I think, as a text on which to hang the few brief remarks that I have been asked to make this afternoon. My Address is entitled "Rheumatism—the value of Research", and so, of course, you may ask me firstly to define the word "rheumatism". Well, most of us cherish some pet ache which we affectionately refer to as "our" rheumatism, but between that sort of thing and the real crippling forms there are many grades.

Professor P. Hench, the leading authority on this subject in America, who was recently over here, told us in the course of one of his addresses that there are over two hundred forms of so-called "rheumatism", and as I am no master of words I propose to evade the issue to some extent by describing to you briefly three typical cases from my records of rheumatism in its most tragic form. I hope that perhaps when you have heard them the need for research may be self-evident to you.

My first case was a child who, at about the time of her seventh birthday, began to run a slight temperature. A few days later she complained of pain in her arms and legs, which were a little swollen. She was thought for several weeks to be suffering from some comparatively trivial complaint, but all this time she was really getting worse and worse. When she first came into hospital her joints were terribly swollen and they had lost their movements; her body was wasted to skin and bone, and she was in constant fearful pain. We were at this stage unable to do much more than alleviate her sufferings, and a month or two later she died. That little girl was suffering from what we call Still's disease—a juvenile form of acute rheumatoid arthritis. I will speak quite candidly and say that we know as yet next to nothing of its cause, and little enough of its treatment. Here is an important field for research and one which, unfortunately, this Council has never had the funds to tackle.

My second case is also, I am afraid, a common story. It concerns a middle-aged widow of the blitz. With a family of children to care for and to cook for, she has to supplement her modest pension by office cleaning, which is a strenuous and somewhat unromantic occupation, but one which can, however, be fitted in at both ends of a busy domestic day. Three years ago her knee started to swell and to ache and now most of her joints are affected. She is forced, of course, to continue her labours, but she actually climbs the stairs to her offices and her home now on all-fours because her knees are unable, unaided, to carry her up. This woman could have been kept going, indeed, possibly cured, had adequate institutional provision been available two years ago. Lord Horder, our Chairman, has put it on record that only about 10 per cent. of such patients who need urgently skilled institutional provision are able to obtain it. Unfortunately in the region in which this tragic case lived there was no such provision, and it is, of course, only a matter of months before she becomes a helpless bedridden cripple.

My third case is somewhat different. It concerns a young naval officer who developed what was thought to be "lumbago" after a course of physical training. This, instead of clearing up as he expected, got worse and worse through the ensuing weeks. He of course tried many forms of electrical and other treatment at the suggestion of his friends, unfortunately all of no avail. Six months after the onset he was unable to leave his bed, and at this stage skilled investigation was invoked and revealed that he was suffering from that type of rheumatic disease known as spondylitis; that is to say the vertebrae of his neck and his spine were fusing into one solid mass. By this time his whole body was completely rigid. If you lifted his head you lifted his body, and all voluntary movement was practically impossible to him. Needless to say his career was finished. He lay there helpless and in pain for a year or two, and then, when even movement in his chest failed, a merciful pneumonia dropped the curtain on his life.

Now these are three selected cases, not by any means of uncommon type. May I just say a few words about some of the other serious forms of rheumatism. Sciatica, neuritis, osteo-arthritis, and neuralgia, are all major enemies of industrial and other life owing to the toll they take of working time and of health. Rheumatic fever comes into rather a different category from all the other members of this group, largely because, as you probably already know, it generally starts with fever and recurs on and off for many years, sometimes indeed throughout life. It has the striking and most unpleasant habit of attacking the heart muscle of its victim. Nearly all the heart disease in this country—and there is a great deal of it—has its origin in this type of rheumatism.

Then there is rheumatoid arthritis which is one of the most terrible scourges our womanhood has to bear—I say womanhood because it attacks that sex with more than five times the frequency that it attacks the male sex. I have already described to you a case of the juvenile form of this disease, but even in its more common form it still prefers to attack the young. This Council has recently been investigating the case of a young woman, aged 25, completely crippled and practically disabled. This disease first attacked her in her late 'teens, condemning her even at this early age to a life of torture and of almost complete inactivity. It is patiently borne, but she is—like thousands of others—completely prevented from playing any constructive part in either personal or public life.

We do not perhaps quite recognize the extent of this problem because these young women "go out of circulation" all too soon, but they are lying in dozens

in their homes and in hospitals all over the country, behind the iron curtain of our indifference. The problem is there and, I think, with your help it is certain of solution by this Council in time.

Osteo-arthritis is also a common and most crippling disease and it mostly affects active and otherwise healthy people in the prime of life. It seems to prefer the larger and weight-bearing joints, which is the contrary to rheumatoid arthritis. It affects many of the leaders in all walks of life, but also, in addition to fibrositis, it affects the industry of this country, and as your Royal Highness has already told us, rheumatism takes a toll from industry of no less than three million weeks of profitable work and costs no less than £40,000,000 every year.

Surely this is something also which it would be wise to subsidize our scientists to look into once and for all. People sometimes ask us why research needs so much money. Is it not, they will suggest, just a question of examining a few patients, carrying out a few tests, and sending in an answer ? I can assure you that it is nothing so simple. It entails constant *assistance* and skilled investigation for years into the causative factors of these disorders, and to ascertain further lines of enquiry into what are really the root causes. Once these causes become evident we begin to investigate methods of treatment ; and these methods again themselves become the subject of similar patient research and enquiry. Infinite patience is required as well as considerable study to perfect all the methods of technique which, intelligently followed in the light of this special knowledge, will one day, I am convinced, bring success.

All this, as you will see, involves continual and costly expense for specially trained research workers and for special laboratory and other equipment, also, if possible, for the establishment of Fellowships for this special purpose.

The effect of success in our research will be twofold. It is, I think, quite obvious to us all how the recovery of active useful life will benefit the individual sufferer. Success will, moreover, also free the great industrial machine from much economic damage and from greatly reduced productivity. It seems to me that rheumatism research should become the " pet charity " of industry ; its contribution to the Empire Rheumatism Council might well be regarded in the light of a worthwhile insurance premium paid to insure the fuller and more efficient working of our industrial machine. (Applause.)

Your Royal Highness, I have perhaps somewhat exceeded the time allotted to me for the few words which I was asked to say on this subject ; but my desire to get to the bottom of this crippling and neglected group of rheumatic diseases obsesses me. If this Council can, in addition to its present all too modest funds, be assured of even half the money which is justifiably spent every year on cancer and tuberculosis and other great social diseases we can get an answer to the problems I have put. We receive sympathy but no financial support from the Government ; so I must appeal most earnestly to everyone here to use their influence with organized labour and with their friends, as I am sure you all do, to help us finance a seven-year plan for this neglected group of diseases. I am sure, Sir, that the results will be dividends beyond our most sanguine expectations. (Applause.)

## TWELFTH ANNUAL REPORT

### NOVEMBER 1947 TO OCTOBER 1948

Your Royal Highness, my Lords, Ladies and Gentlemen,—On behalf of the Council it is my humble duty to express sincere gratitude to His Majesty the King for so generously permitting the twelfth Annual General Meeting of the Council to be held in the State Rooms of St. James's Palace.

It is also with great pleasure that I express to Your Royal Highness the appreciation of the Members of the Council and others here to-day for presiding over the Twelfth Annual General Meeting. The Council recalls with deep satisfaction the previous occasions on which Your Royal Highness has presided over our meetings, and also the message of good wishes received last year during Your Royal Highness's term of Office as Governor-General in Australia. This continued expression of Your Royal Highness's interest in our work is a matter of the greatest encouragement to us.

It is with deep regret that I record the loss, during the past year, of two Vice-Presidents : Major Sir Frank H. Bowater, Bt., T.D., and Sir Alexander Maclean, both of whom have given liberally of their resources and service to further the work of the Council. The generous gift of the late Sir Alexander Maclean of £10,000 enabled the Council in 1937 to establish its first Research Laboratory at the Hospital of St. John and St. Elizabeth, and a tablet bearing Sir Alexander's name commemorates what might well prove to be a milestone in the history of rheumatism research.

It is my pleasure to lay before the Council this record of progress during the year 1947-8, and in doing so I cannot praise too highly the services rendered by the members of the Executive, Finance, and Scientific Committees. Each member has responded liberally to the demands made upon his time and experience, and our cause owes a debt of gratitude to them which could not be estimated in terms of monetary value.

The year just concluded has not been without its difficulties, both from the scientific angle and from the viewpoint of finance, but a survey of the year's endeavours shows a record of achievement which is deserving of approbation.

#### Research

This remains our paramount duty. The full-scale investigation into the causation of rheumatoid arthritis,

referred to in my Report last year, has continued assiduously during 1948, and several experienced registrars have contributed to the detailed analysis of cases and controls which go to make up the data upon which the analytical statistician Dr. Lewis-Faning will frame his first report of conclusions. This Report is awaited with deep interest by the scientific committees of the Council, for from it may be revealed information which will determine what future lines of research are most promising.

We have also, during the past year, continued with our research work into the allergic aspects of rheumatism at the Council's laboratory at the Hospital of St. John and St. Elizabeth. Through the generosity of an anonymous donor we were enabled to re-open this laboratory last year after its enforced closure during the late war. The work, therefore, made possible in the first instance through the generosity of the late Sir Alexander Maclean has been re-commenced. Research into that specific aspect of rheumatism at the laboratory is being vigorously pressed forward.

A still further endeavour in the field of rheumatism research has recently been undertaken by the appointment of a technical assistant to the rheumatic unit at the Univeristy of Edinburgh. This effort is made at the instance of Professor Davidson, Chairman of the Scientific Advisory Committee, and is under his able guidance.

Dr. Savage and Mr. Hindenach are undertaking a short investigation into the cause of rheumatic pain in the shoulder and the results are awaited with interest.

It has been an innovation of the year that members of our Research Sub-Committee should periodically visit centres of research throughout the country in order to keep fully appraised of the latest provincial developments in the field of Rheumatism. These periodic visits afford a valuable insight into new methods of research and treatment formulated, and in active use, at the various centres throughout the Kingdom.

### Treatment

Financial contributions to the Rheumatism department of the West London Hospital have continued with the assistance of the Boroughs of Kensington, Hammersmith, and Fulham on the same level as in 1946-7. Additionally, at the request of the Borough of Hammersmith facilities were initiated for the arrangement of a peripheral clinic to be held twice a week at the Westway Centre.

Payments from the Scottish Fund to Professor Davidson for his Department in Edinburgh have again been renewed.

Many new methods of treatment and claims of " cures" have been received during the year. These have all been submitted to the Research Sub-Committee who have given much time and thought to the various claims submitted. The Committee is ready at all times to place the benefit of its experience and advice at the disposal of any *bona fide* organizations and persons who feel they have a contribution to make in the matter of treatment and research.

The Council, through the members of its Research Sub-Committee has recently issued a standard case sheet for the rheumatic diseases. This important recording unit has been laid before the Ministry of Health, and hospital rheumatism departments throughout the country are being furnished with the unit to assist their diagnosis and treatment facilities. It is pleasing to record that the standard case sheet has been sent, upon application, for utilization in America, in South Africa, and in New Zealand, and it may conceivably be, in a short measure of time, the accepted case sheet for world rheumatic practice.

### Education

The Education of postgraduates and general practitioners in the field of research and treatment is considered by the Council to be of vital importance in maintaining an efficient and up-to-date rheumatic personnel throughout the country. It is in pursuance of this resolve that the Council has, during the past year, increased its lecture course at the Apothecaries Hall, and it is satisfying to record that the Council's endeavours in this regard have been well-repaid by the attendance of large numbers of graduates and general practitioners from all parts of the country.

To emphasize the importance placed by the Council in the matter of continuing education, enquiries were instituted amongst the Deans of the medical schools throughout the country and to the Chairmen of the regional hospital boards, as the Council is desirous of stimulating an expansion of medical education on our specialty. The replies received are the subject of discussion by our Education Sub-Committee. It is considered by the Ministry of Health to be vital that men trained in the rheumatic diseases should be available in increasing numbers.

In response to applications received from bodies and organizations interested in rheumatism, including the Section of Odontology of the Royal Society of Medicine, specialists from the Council's panel of lecturers have given scientific audiences the benefit of their experience and advice.

At the request of the Central Council for Health Education a representative of the Empire Rheumatism Council was nominated to serve as the Council's representative on that body.

The Council continued its financial contribution to The Royal Society of Medicine to extend its library of scientific and medical books on the rheumatic diseases.

*The Annals of the Rheumatic Diseases* has been published regularly during the past year. It contains a symposium of research activities into the causative factors and treatment of the rheumatic diseases, and is the standard publication on all matters affecting rheumatism. Its circulation is world-wide.

The year, therefore, in the matter of research, treatment, and educational endeavour has been one of great activity and progress.

### Relations : Abroad

*Canada.*—In consequence of communications with Dr. Wallace Graham, President of the Canadian Arthritis and Rheumatism Society, an application for affiliation of that Society as an autonomous branch of the Empire Rheumatism Council has been received. The application

which has the support of the Canadian Ministry of National Health and the Canadian Medical Association, is further evidence of the close co-operation of that Dominion with the mother country in the field of rheumatic endeavour. We are indebted to Sir Walter Kinnear, Chairman of the Finance Committee, for the valuable contacts he made during his recent visit to Canada on the Council's behalf and which have had such a favourable result.

*Australia and New Zealand.*—The Council is indebted to Dr. C. B. Heald who, like Sir Walter Kinnear, devoted some part of his visit to these Dominions to the interests of the Empire Rheumatism Council. It is due to his kindly interest that headway was made in the matter of encouraging the Australian and New Zealand Medical Authorities to become affiliated with us. An application from the Royal Australasian College of Physicians for affiliation of a Council to be nominated by them as an autonomous Branch of the Empire Rheumatism Council is brought much nearer. It has been a privilege recently to welcome to this country Dr. C. G. McDonald, Vice-President and late Honorary Secretary of that College. Dr. McDonald's interest in the extension of co-ordination of effort in the field of Rheumatism has made no small contribution to the development of these good relations.

A two-day Meeting is being held in Rotorua, the Spa Centre in New Zealand, on Nov. 18 and 19 next to inaugurate the New Zealand Branch of the Empire Rheumatism Council.

*European League Against Rheumatism.*—The Council has continued to support financially the work of the European League, for it is essential that we keep abreast with all remedial measures affecting the rheumatic sufferer. Moreover, a recent summary of the work of the Danish League against Rheumatism, linked with this Council through the European League, reveals much beneficial legislative activity in the Scandinavian countries.

As in 1946-7, many of our members have been invited to attend the International Congress on Rheumatic Diseases to be held in America in the Spring of 1949. Papers have been submitted by several members of the Council towards the Congress Agenda.

*Administration.*—In accordance with usual practice it is recommended for your approval that the key administrative Committees, viz. Executive Committee, Finance Committee, and the Scientific Advisory Committee, be re-elected for 1949. The Committees here referred to give generously of their time and service in a voluntary capacity, and the Council is fortunate to count among its members men who are well-versed and highly placed in the respective spheres in which they labour so diligently in our interests.

Realizing to the full extent to which the rheumatic diseases affect the conduct of our daily lives and national affairs, the Scientific Advisory Committee during the year reorganized its constitution on an extended basis, and there has emerged as the result a strong and competent Research Sub-Committee and an Education Sub-Committee, both of which have been functioning regularly during the latter half of the year. These Committees now have a greater opportunity of considering the many problems of research, investigation, and treatment which are constantly being submitted to the Council from many channels.

*The Future.*—It is not within my power of discernment to estimate what the year 1949 holds in store for us. Suffice it to say that from the Members of the Empire Rheumatism Council there is an abundance of talent ready to come to grips with all rheumatism problems with which they may be confronted. There is also available I am sure, a spirit amongst our many honorary members and interested persons which can be relied upon to assist in providing the necessary finances for the continuation and expansion of our work. Rheumatism research is a costly business, and we continue to rely as heretofore upon the generosity of public philanthropy to assure that our labours for the benefit of all rheumatic sufferers over the past twelve years shall not be cast away. Remaining un-nationalized and free from control, the Council looks confidently for the necessary voluntary financial support to continue, and, if sufficient funds are available, to expand its present activities. The Report of the Finance Committee tells how wisely our income has been expended and how urgent is the call for greater help. HORDER

# HEBERDEN SOCIETY

A General Meeting of the Society was held on Dec. 3, 1948, at 11 Chandos Street, London.

Dr. Heald (Royal Free Hospital) contributed the first paper entitled "Setting-up the Disabled". This dealt with the invalidity due particularly to rheumatism: it outlined weaknesses in existing procedures, the general problems facing society, and suggestions for dealing with them. (This paper is to be published in full elsewhere.)

Dr. Jacques Forestier, the Honorary Corresponding Member from Aix-les-Bains, talked on "Comparative Indications and Results with Gold and Copper Therapy" (published in full at p. 132 of this issue).

Dr. Brandon Lush (introduced by Dr. Ernest Fletcher, Royal Free Hospital) outlined some basic principles in the treatment of flexion deformity of the knee. The causes of this deformity in rheumatoid arthritis, he said, were, first, that this is the position of most comfort; secondly, in acute cases muscle spasm immobilizes the joint in this position; thirdly, with muscle wasting the extensor muscles are affected more rapidly and more completely than the flexors; fourthly, with an effusion this is the position of greatest capacity. These four factors in any particular case are of varying importance. Prevention consists of full explanation to the patient, the use of back splints in the position of optimum function (5° of flexion) and complete daily movements together with the maintenance of muscle function. He did not think that muscle spasm was important, nor its treatment by prostigmine. The treatment of established deformity is either arthrodesis in 5° of flexion for the severe case,

or plaster rest in acute stages and correction of the flexion deformity by the following controlled technique under pentothal anaesthesia : with the leg extended between two tables and covered with stockinet a plaster back slab is applied and a sling passed over the top of the knee and attached below it to an extension apparatus (motor-car jack). A controlled extension of the knee is then carried out by turning the handle of the jack with the operator's hands on the knee. Plastering is then completed and the patient returned to bed for forty-eight hours, following which bivalving is done and physiotherapy started. In discussion, the dangers of dislocation were mentioned.

Dr. Duncan Shiers (introduced by Dr. Copeman, West London Hospital) dealt with chorionic gonadotrophin from pregnant mare's serum in the treatment of rheumatoid arthritis. He said that of the three secretions of pregnancy, oestrogen, progesterone, and chorionic gonadotrophin, the two former have been tried without success in the treatment of rheumatoid arthritis. The author, investigating the third, has used " pregnyl " (luteinizing) and " gestyl " (follicle-stimulating and luteinizing hormone prepared by Organon Laboratories). Two hundred units on the average were given daily by intramuscular injection without other drugs. Diminution of pain and stiffness was noticed after the fourth injection, together with a sense of improved well-being. The injections were continued for two to three weeks (about 5,000 units) and then on alternate days. Seven case histories were given illustrating the marked improvement, which was sustained for a period of months following discharge. Four of the seven cases had had natural pregnancy remissions. No complications were noted other than some alteration of menstrual cycle.

Dr. Kathleen Lawther (introduced by Dr. Ray, British Red Cross Clinic) talked about the use of procaine and lactic acid injections in degenerative joint disease of the hip. She summarized the results of treatment in sixty-four cases. There was marked relief of pain in a proportion of these, but very few showed greater range of movement. There were similar results in a small series using 2 per cent. procaine alone.

Dr. G. Watkinson (introduced by Professor Tonbridge, Leeds) talked on massive salicylate therapy in rheumatic fever in young adults ; the effects of small and large dosage on clinical manifestation, carditis, and sedimentation rate were discussed. (This paper appears at p. 120 of this issue.)

A Clinical Meeting of the Heberden Society was held at the Rheumatology Department of the Royal Free Hospital on Jan. 7, 1949.

After an introduction from the outgoing President, Mr. S. L. Higgs, Dr. W. S. C. Copeman occupied the Presidential chair. He paid a warm tribute to Mr. Higgs for the excellent conduct of the Society's business during the previous year, which had seen a remarkable increase in numbers, activities, and influence.

Dr. Ernest Fletcher introduced three clinical cases. The first was a man with Reiter's syndrome ; the second one with pulmonary tuberculosis and multiple joint involvement of a rheumatoid nature, together with gross destruction of the right humerus. Opinions were divided as to whether this latter joint was rheumatoid or tuberculous. The third case was a man with unusually large cystic nodules or bursae over both olecranon bones.

Dr. J. S. Lawrence, of Walkden, Lancashire, introduced by Dr. J. H. Kellgren, Manchester, gave a short paper on " Differential Plasma Viscosity " in various diseases. By means of a salting-out procedure, viscosities of various protein fractions were measured in an Ostwald's viscosimeter at various times during the patient's illness. After correction for the viscosity of the salt solution, these figures were expressed numerically and the various fractions (fibrinogen, gamma-globulin, alpha- and beta-globulin, and albumin) were shown to have viscosities characteristic of the stage of the illness and running parallel with the expected quantitative changes in those fractions.

After discussion of several of the specimens and microscopic slides shown by Dr. Lush, Dr. Bryan, and Dr. Buchan, the meeting adjourned.

At a meeting of the Heberden Society on Friday, March 4, 1949, at 11 Chandos Street, London, W.1, with Dr. W. S. C. Copeman in the Chair, a discussion was held on the question, " Is Electrotherapy Empirical ? " There were fifty-one members and guests.

The opener, Mr. C. W. Marshall, speaking as an interested layman, contrasted German and English practice in the use of ultra-violet light as an example of the antiquated and empirical use of physical methods in England. He was critical of the numerous eponymic " currents ", and said that all electricity used could be described in terms of linear and exponential functions. Although English school textbooks on electricity were good, the less said about English medical electricity textbooks the better : at best they were picturesque.

Dr. P. Bauwens, replying, said that while in part he agreed with Mr. Marshall's criticisms, many of these were not justified. We did know a good deal about the action of direct and high- and low-frequency alternating currents : he saw no reason why " galvanic stimulation " should not be used by the doctor in the same way as " galvanized iron " is by the engineer. Equipment was in many places crude, due to lack of money, but it did its job. Measurements of the current were usually adequate, but some needed the co-operation of electrical engineers, for example, the measurement of tissue temperature in a high-frequency field. He thought Mr. Marshall failed to appreciate the complexity of biological phenomena : heating a brick was one thing ; heating a living leg might produce its therapeutic effects psychologically or by vasodilation, or even possibly by direct heating.

After some discussion by Dr. Cooksey and Dr. Shiels, Dr. Tegner summed up : the meeting will have been of value if out of it there comes a closer co-operation between experts in the physical field and those working on human beings.

# BOOK REVIEW

*Annual Report, 1948, of the Department of Rheumatic Diseases, West London Hospital.* Illustrated. Pp. 40. No price given.

The Department of Rheumatic Diseases of the West London Hospital has celebrated the completion of ten years of important and valuable work by publishing its annual report for the first time in printed form for general circulation. It differs from the usual form of a hospital report in that it limits the usual statistical details but gives an account of the work of the department since its foundation by Dr. W. S. C. Copeman, with the collaboration of the Empire Rheumatism Council and the financial support of enlightened municipalities, first Kensington, and later Hammersmith and Fulham.

The scope and usefulness of the department has grown greatly, especially since the end of the war, and an interesting account of the development and the methods is given. It is hoped that this will act as a guide and stimulus to similar departments which should rapidly increase in numbers and spread all over the country. Many similar schemes are being planned, but especially in the provinces they have not yet got beyond the " blue print " stage ; those in the spas, with a long history, may learn from this comparative newcomer in the campaign against the national scourge of rheumatism.

The report gives an account of the work done and the methods employed ; there are interesting reports by members of the staff. An article by Dr. Copeman on the medical history of rheumatism is followed by others of technical character by Dr. Philip Hench of the Mayo Clinic (U.S.A.), and Drs. Wrigley, Highton, and Mason, which give the Report a scientific value in marked contrast to the usual kind, and make it a valuable addition to a doctor's bookshelf. C. W. BUCKLEY.

# CORRESPONDENCE

## Pain in the Arm : a Review

SIR,—In his review of the syndrome of pain in the arm (*Annals of the Rheumatic Diseases*, 1948, 7, 15), H. L. Hoffman seems to attach the greatest importance to those diseases responsible for this syndrome arising in the spinal cord, intervertebral foramen, and thoracic outlet. The author has, I believe, under-estimated the peripheral causes, especially those of muscular origin.

In 1938 I defined " myalgia " (myopathy) as a muscular disease localized in anatomical parts of a muscle and/or its appendages, viz. tendon ligaments, etc. In contradistinction to " tender spots "—a purely *subjective* sign—supposed to be characteristic of fibrositis, the diagnosis of myalgia was based on *objective* criteria, viz. " myalgic spots ", which are responsible for *referred pain*. These are localized muscular areas, harder to the touch than the surrounding parts (that is, they are in a spastic condition), which on pressure produce agonizing pain accompanied by involuntary, reflex-like jerking, an objective and pathognomonic sign.

Under the term " idiopathic myalgia " (Good, 1940) two cases of pain in the arm were described which, by reason of the symptoms present (paraesthesia, numbness, pins and needles), mimicked neuralgia or " brachial neuritis ". The diagnosis could be proved by injection of procaine, which cured the disease. Independently in 1938 Sir Thomas Lewis and Kellgren proved that injection of a hypertonic saline into a muscle may cause referred pain.

According to Hoffman the neurological symptoms in spondylitis and osteo-arthritis are caused by root involvement. In the former the symptoms occur in the early stages of the disease, by reason of epidural and periradicular exudate. They are not due to bony narrowing of the intervertebral foramina and are much less common when the spine has become fixed. In osteo-arthritis of the spine root symptoms and signs are more common. These signs arise before demonstrable osteophytes are present, or they may occur only after osteo-arthritis has been present for years. The signs and symptoms present (pain, paraesthesia, muscle weakness, increase of pain on movement) have been described as characteristic of myalgia (Good, 1938), and it was stated that rheumatoid and osteo-arthritis are often associated with myalgic conditions. The question whether the complaints mentioned are caused by a root lesion or myalgia is important from a scientific point of view, but even more so for practical therapeutics. If a mono- or polymyalgia is responsible, the complaints can be fully relieved by objective location of the myalgic spots and accurate and thorough injection of a few c.cm. of procaine into each spot. Hence the injection serves as a diagnostic test in additon to the curative effect.

Walshe has recently drawn attention to the frequency of the common syndrome of acroparaesthesia in the arms and fingers of middle-aged and elderly women. He came to the conclusion that the complaints are caused not by neuritis—with which I agree—but by a sagging of the shoulder girdle. However, in my experience the syndrome is due to myalgia of the elbow and can rapidly be cured by an appropriate procaine injection.

When Hoffman states that root symptoms in osteo-arthritis may cause headache (1-3 cervical root), that tender nodules may be associated with nerve root irritation, and that such cases are wrongly diagnosed as of primary " fibrositis " he, in my opinion, puts the cart before the horse. As stated above, the diagnosis of myalgia (not fibrositis) has to be made objectively ; and procaine injection will prove conclusively whether or not the diagnosis is correct. But there is not such a test for root lesions at present.

I should like to plead that the term " fibrositis ", which is a misnomer, should be dropped, and that the term " myalgia ", as defined in 1938 and based on scientifically satisfactory criteria, should be used. The great frequency of myalgia will not appear surprising if we consider that the skeletal muscles represent the largest organ of the body—the active locomotor apparatus —that they amount to 40 or 45 per cent. of the organism in weight, contain up to a third of the total blood, and are subject to wear and tear during working hours.

I am, etc.,

London, N.W.3. M. G. GOOD.


REFERENCES

Good, M. G. (1938). *Brit. J. phys. Med.*, N.S., 1, 302.
—— (1940). *Lancet*, 2, 326.
—— (1941). *Practitioner*, 146, 167.
—— (1942a). *Ibid.*, 148, 236.
—— (1942b). *Ann. rheum. Dis.*, 3, 118.
Hoffman, H. L. (1948). *Ibid.*, 7, 15.
Walshe, F. M. R. (1945). *Brit. med. J.*, 2, 596.

# NEWS ITEMS

### International League against Rheumatism

Dr. J. van Breemen, Hon. Secretary of the International League against Rheumatism, has recently circulated, from his offices at Keizersgracht 489, Amsterdam, a short report covering the period from December 1939 to June 1948.

Some months before the German occupation of the Netherlands Dr. van Breemen realized that it would be impossible for his country to remain neutral, and as it was impossible to consult the whole council of the League, he, in concert with Dr. Ralph Pemberton, advised all national committees that the League could not continue its activities. After the occupation Dr. van Breemen was asked by the Germans to move the Bureau of the League to Germany and to hand over the files, but he was able to inform the authorities that the League had discontinued its activities. The files were hidden for some years and were afterwards found badly damaged.

Soon after the liberation in May 1945 Dr. van Breemen received many letters asking whether it was not possible to restart the work of the League. Although he felt that the younger generation should now take over the work, he decided that it was in the interests of international co-operation that he should continue in office at least for the time being, in order to discover how much remained of the old national committees. In the report he expresses a wish, however, to uphold his original decision to resign in favour of a younger member, and he hopes that this matter will come up at the New York Rheumatism Congress in the summer.

Death had taken its toll of many officers and members, for example, Dr. Fortescue Fox, for many years President of the League. According to reports from Moscow it appeared that Professor Kontolovsky, Vice-President of the League, has died. The second secretary, Professor Gunzburg, from Antwerp, was carried off to Germany and killed. Professor Kahlmeter, the Swedish representative, was obliged to resign because of serious illness. Professor Pap Lajos is no longer in Hungary. These are all heavy losses, and the only remaining Council members are : Dr. R. Pemberton, Philadelphia, President ; Dr. J. van Breemen, Amsterdam, Hon. Secretary ; Prof. Dr. B. Prusik, Prague ; and Dr. W. S. C. Copeman. It was decided, however, that no new members of the Council should be elected until a meeting of the members of the League could take place ; this has been arranged to coincide with the New York Rheumatism Congress in June 1949.

It occurred to Dr. van Breemen to found a European League against Rheumatism, following the example of the Pan-American League which had been founded during the war, and functioning under the auspices of the International League against Rheumatism. This idea was taken up with sympathy in many European countries. The Danish Committee against Rheumatism undertook the work of the Secretariat and organized a congress which took place in September 1947. The relationship between the European and the International Leagues was regulated legally, while the Secretariat of the European League communicated directly with the national committees in Europe. The Secretariat of the International League has the task of maintaining international contacts, and also of keeping in touch with the United Nations Organization and other official bodies. The care of the international library is also entrusted to it. Members of the council of the European League were elected at Copenhagen as follows : *President*, Dr. Mathieu-Pierre Weil, Paris ; *Vice-Presidents*, Prof. F. Lenoch, Prague, and Dr. W. S. C. Copeman, London ; *General Secretary*, Professor E. Jarløv, Copenhagen ; *Secretary*, Dr. K. Kalbak, Copenhagen ; *Treasurer*, Mr. O. de Bornemann, Copenhagen. Dr. R. Pemberton and Dr. J. van Breemen, respectively President and Secretary of the International League against Rheumatism, were also elected Council members.

The Danish Committee against Rheumatism, and also the American Rheumatism Association, have sent money to the International League to enable the expenses of the Bureau for 1946 and 1947 to be defrayed.

At the New York Congress one or more meetings will be devoted to the reconstruction of the International League. There appear to be two possibilities. The first is to return to the pre-1940 situation when there were both national committees and individual members. The second is to retain the scheme forced upon them in 1940, with a Pan-American, Pan-European, and later a Pan-Asiatic, Pan-African, and Pan-Australian League, all under the aegis of the International League against Rheumatism. In this set-up there would be no personal members of the League, but only national committees of the different countries. Dr. van Breemen says, "It would appear to your secretary . . . that under the present circumstances the maintenance of a Pan-American and a Pan-European League, in spite of the objections attached to it, will be the best solution possible for the working of an International League. The great activity and the excellent organizational capacity shown by the Copenhagen Secretariat make it desirable . . . that for some years at least the Secretariat of the European League shall remain at Copenhagen."

Dr. van Breemen stresses the need for an international rheumatism journal, and mentions welcome concessions made by the *Revue du Rhumatisme*. In this connexion it should be pointed out that the *Annals of the Rheumatic Diseases*, which Dr. van Breemen does not mention, has already become affiliated to most of the national and international rheumatism associations with representatives on its editorial board, and is publishing articles from America and from the Continent of Europe, with summaries in French and with an abstracting section covering the world literature.

### New York Rheumatism Association

A Clinical Conference was held by the New York Rheumatism Association at the Hospital for Special Surgery, New York, on Dec. 1, 1948, under the Chairmanship of Dr. Otto Steinbrocker (Co-chairman, Dr. Cornelius Traeger). Papers on gold dermatitis were read by Dr. Bernard Rogoff and J. Lankin, and on gold therapy by Dr. Marjorie Patterson. Rheumatoid arthritis in infancy was dealt with by Dr. Jacques Durivage, Two cases of scleroderma by Dr. Willard Squires, arachnodactyly by Dr. Emanuel Rudd, calcium deposition in periarticular structures following massive vitamin D dosage by Dr. Willard Squires, and quantitative studies of lauron deposits in tissue obtained from autopsies by Dr. Bernard Rogoff.

A Clinical Conference was held at the Welfare Hospital Dispensary on Jan. 5, 1949, under the Chairmanship of Dr. Otto Steinbrocker (Co-chairman, Dr. Jed H. Irvine). Muscular rheumatism was dealt with by Dr. Sydney Margolin (by invitation), elbow injury with subsequent hand disability by Dr. Herman Dworzan, and apparent reflex sympathetic dystrophy following injury by Dr. Jed H. Irvine.